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Contents

The Resource for concurrent biological computing aims at advancing the state of the art in biological sciences and addressing contemporary health issues through computational molecular biology. Determining the structure and function of biomolecular aggregates, consisting of membranes, bioenergetic proteins, DNA, and other biopolymers, is critical to understanding the processes involved in disease, as well as for drug design and effective drug delivery. Computational modeling can be used effectively to this end, to complement laboratory research. The size of aggregates of interest and the time-scales of simulations required make modeling a computationally demanding task. The Resource aims at harnessing the power of parallel computing for this task.

The Resource develops theoretical formulations applicable to large aggregates and numerical algorithms that allow faster simulations. It develops parallel algorithms that can efficiently utilize the available computing power, and scale up to utilize the larger parallel supercomputers of the future. It embodies these algorithms in software for running and interactively controlling simulations and visualizing their results. The software is periodically released to the larger community via the Internet. The Resource also maintains a state-of-the-art computational laboratory and engages in demanding collaborative research projects.

The Resource has created MDScope, an efficient, modifiable and integrated package for structural biology research. MDScope includes NAMD, a parallel molecular dynamics program, and VMD, an interactive visualization and analysis program. During the past year, capabilities of both NAMD and VMD were significantly enhanced.

VMD has undegone a number of improvements over the last year. Static docking and structure alignment features were added which permit observations of different molecular interactions. VMD's scripting language was extended, allowing analysis routines to be written without recompiling VMD. As an example, these enhancements enable scientists to use VMD to produce animated illustrations and tutorials about their research. The free availability of VMD's source code, combined with its capabilities and modifiability, is turning VMD into a popular and mature visualization environment for structural biology.

NAMD is a parallel molecular dynamics program, developed with the goal of effective parallelization from its inception. It is written in C++ using object oriented techniques, with the intent of making it easy to modify for experimental purposes. During the past year, several optimizations were incorporated in the software to effect a three-fold reduction in computation time for each simulation timestep. Algorithmic improvements, including constrained hydrogen bond-lengths and an improved scheme for multiple timestepping which allows less frequent computations of long-range interactions, led to a further 2.5-fold speedup for each femtosecond simulated. A new data structure reduced the memory requirement of NAMD by 60 percent, enabling for the first time a simulation of the full poliovirus coat, consisting of over 590,000 atoms. NAMD was used in several large

simulations for the first time, including a study of the estrogen receptor hormone, and for computational studies of micromolecular manipulation of biomolecules. The latter, which involves pulling biomolecules in an aggregate apart by applying external forces, was especially remarkable as it demonstrated the modifiability of NAMD.

The Resource has begun the development of the next generation molecular dynamics program, NAMD 2, using the performance improvement opportunities identified during the past year of NAMD's use. NAMD 2 uses a new parallel structure that will improve its performance, and allow it to effectively utilize parallel computers with hundreds of processors. Also, based on new parallel programming techniques, NAMD 2 is much more modular, making it easy to modify and experiment with its individual components. A preliminary version of NAMD 2 has been completed and already exhibits better performance than the original version of NAMD.

The Resource was one of the first computational groups to employ workstation clusters for parallel simulations. During the past year, the Resource expanded the cluster with four four-processor SMP HP workstations, connected by a high bandwidth ATM communication network. NAMD was adapted to the cluster environment, and was used for several simulations. Coupled with the the acquisition of four SGI Indigo Maximum Impact workstations, and the existing 3D projection facility, the Resource is now exceptionally well equipped with a balanced and powerful computational environment.

The Resource continues to develop new methods and theoretical formulations that facilitate understanding of large biomolecular aggregates. Binding and unbinding of biomolecules is at the heart of most biological processes. Recently, micromanipulation techniques such as atomic force microscopy (AFM) have been used effectively in laboratories for small molecules, to investigate the unbinding process. The Resource has developed a similar computational approach, Steered Molecular Dynamics (SMD), for studying large biomolecules. Forces are applied in a chosen direction to selected parts of a biomolecular assembly to facilitate its unbinding. The data obtained as a result of such simulations is analyzed using MDScope to identify structural elements of the assemblies that play key roles in the process of unbinding. This technique was applied to the avidin-biotin complex, bacteriorhodopsin, and phospholipase A2 systems. In the latter case the technique permitted the extraction of lipids from membranes, by applying forces to the head group of a lipid so that it is pulled into the catalytic site of the phospholipase enzyme.

A recent survey of protein domain movements revealed that hinge-bending movements, where rigid protein domains are connected by flexible joints, are the dominating type of protein conformational changes documented in the Brookhaven Protein Data Bank [1]. Hinge-bending is also believed to allow an induced fit of molecular surfaces in protein assembly and ligand docking. Based on this concept we have developed the algorithm *Hingefind* to investigate protein domain movements by comparing two conformations of

a protein. The algorithm partitions the protein into rigid domains of preserved packing and subsequently identifies the effective rotation axes (hinges) of the relative movement of the domains. The identification of hinge axes and their corresponding rotation angles provides a reduced representation of the complex movements exhibited by proteins.

Studies of large biomolecules would not be possible without the methods and the software developed at the Resource. Many collaborative projects (mainly with experimental laboratories) that utilize the large scale simulation capabilities at the Resource are in progress. Some of the recent collaborative projects are summarized below.

Apolipoprotein A-I Reconstituted HDL particles consist of a phospolipid bilayer disk surrounded by two apolipoprotein A-I molecules. Their structure has not been determined experimentally. Using available experimental data, a major part of the structure has been predicted and tested computationally for stability by simulated annealing.

Cytochrome C Oxidase This respiratory enzyme reduces molecular oxygen to water and pumps protons across a cellular or mitochondrial membrane. Beginning with experimentally determined structures, the pathways of the substrate oxygen and of the protons were studied using molecular dynamics with locally enhanced sampling. This has resulted in a proposal for a new mechanism for proton transport.

Architecture-specific protein–DNA The structure of the complex consisting of DNA and the chromosomal protein, HMG-D, was predicted by docking previously known structures of individual HMG-D and DNA, and by simulating the resultant system in salt water.

Sequence specific protein–DNA The estrogen receptor is a transcription factor controlled by estrogenic hormones. To understand how the estrogen receptor regulates gene expression, simulation studies were undertaken, using the program NAMD on the Resource's workstation cluster. The simulations suggest that the transcription-factor repositions DNA on the nucleosome by bending and unwinding the DNA, placing the TATA box in the linker region where it is accessible to the activity of further transcription factors.

Calmodulin Calmodulin belongs to a class of calcium-binding proteins that regulate processes such as smooth muscle contraction and sliding filament motion in skeletal and cardiac muscle. A 3 ns simulation of the protein in aqueous solution revealed calmodulin's conformational flexibility suggesting a time-dependent availability of target-peptide binding surfaces.

Cell-Motility Proteins Adenosine triphosphate (ATP) is the source of metabolic energy which drives cell motility proteins. Our research was concerned with the fundamental structural processes which allow living organisms to move, namely, the mechanism of ATP-recognition and the response to ATP-hydrolysis. Specifically, we modeled the unbinding of phosphate after ATP hydrolysis in the cytoskeletal protein actin and nucleotide-dependent movements of the kinesin motor.

Modeling of the Bacterial Photosynthetic Unit The Bacterial Photosynthetic Unit (PSU) constitutes a large protein complex that is highly efficient in absorbing light, fueling its energy into the metabolism of photosynthetic bacteria. To understand the mechanisms of light absorption and energy transfer within the PSU, structural information of each protein component as well as information on the overall assembly is required. Resource investigators have modeled the atomic structure for the light-harvesting Complex I which directly surrounds the photosynthetic reaction center and, together with several copies of light-harvesting Complex II (LH-II), forms the PSU.

Poliovirus Coat The poliovirus is a small, non-enveloped single-strand RNA virus. The Resource studies the poliovirus by means of MD simulation, in particular: the role of ligands for the stability of the virus capsid and the role of key residues in the conformational rearrangements of the virus.

The Resource has served the community of biomedical researchers at UIUC as well as elsewhere, through its software, facilities, collaborations and training efforts. The 3-D projection facility of the Resource is often utilized by researchers from Illinois, by visitors to the Resource, and by students in Physics, Biophysics and Chemistry classes. A seminar series run by the Resource brought over 25 renowned researchers to the campus community. The Resource organized several workshops and conferences, such as a 1-day workshop on using VMD and a 2-day conference bridging the gap between experimental and computational researchers in structural biology.

The Resource distributes its software package MDScope, with the programs NAMD and VMD widely via the World Wide Web. As of June 1, 1997, NAMD had been downloaded 981 times and VMD 2,663 times.

The Parallel Molecular Dynamics Program NAMD

MDScope is an integrated computational environment for structural biology, with an object oriented design implemented in C++. It supports fast simulations of large biomolecules (over 100,000 atoms) using parallel computers. The visualization component, VMD [2] allows users to control the simulations interactively and to see simulation results. NAMD [3], another component of MDScope, is a parallel molecular dynamics program.

Understanding the behavior of an interesting biomolecule typically requires simulations of millions of one femtosecond timesteps. Only a highly efficient program can accomplish this in a reasonable time. During the past year, we have engineered several performance improvements in NAMD. Efficiency enhancements were attained by a combination of new numerical algorithms and improved programming techniques.

NAMD users benefit from advanced numerical algorithms that exploit multiple time and space scales to run simulations in less time. The first version of NAMD to be released—NAMD 1.3 in July 1995—employed an enhanced parallel fast multipole algorithm developed at Duke University [4]. It also uses a multiple time-stepping scheme to perform the most time-consuming computations less often. Version 1.5, soon to be released, achieves even better performance by freezing covalent hydrogen bond lengths and by replacing the 12-term fast multipole algorithm with an 8-term improved fast multipole algorithm, also developed at Duke.

During the last year we have incorporated into the NAMD program several optimizations aimed at reducing both time and memory requirements. The memory requirement of the program is dominated by the lists which store all pairs of atoms within a certain distance. By optimizing the representation of the pairlists, we reduced the overall memory requirement by 70 percent. As a result we were able to achieve the simulation of a 590,000 atom poliovirus coat. To reduce execution time, we employed precomputations of commonly-needed coefficients, which, along with other optimizations, led to to a 60 percent reduction in execution time for typical cutoff simulations. For example, execution time for a 15,000 atom protein and water system dropped from 26 to 9 seconds per timestep. These optimizations will be part of NAMD 1.5.

Recently, we have started development of a next generation program, NAMD 2. The major modules of this program are written in Charm++, a C++ based portable parallel programming language. NAMD 2 divides the set of atoms into multiple cubes. Each cube is represented as a parallel object in Charm++. Such parallel objects can be freely assigned to different processors, thus achieving a spatial decomposition of the computation. Most of the computational work involves computing forces between atoms in neighboring cubes. NAMD 2 treats these interactions themselves as objects that can be freely assigned to processors. This creates a larger number of objects, allowing a load balancer

to distribute the computational work evenly across processors.

Coding a parallel molecular dynamics program with multiple objects per processor is complex. The code expressing parallel coordination and data exchange can interfere with the clarity of the code expressing the numerical algorithm, and vice versa. By utilizing both multithreading and message-driven objects, NAMD 2 clearly separates the parallel logic from the numerical code. As a result, NAMD 2 is easier to understand, maintain, and modify than the earlier versions of NAMD. By using a multilingual parallel programming framework [5], the program can use libraries written in other parallel languages, and thus was able to incorporate the PVM-based parallel fast multipole library used by NAMD 1.3-1.5. The new program has been ported to a cluster of HP workstations and the new SGI Origin2000 parallel computer, and tested with as many as 16 processors. We expect to port it to other parallel machines including the Cray T3E, and to demonstrate its performance on 100 processor machines in the near future.*

		Processors				
Simulation		1	2	4	8	16
ER-GRE (37,000 atoms)	Time	7.2	4.0	2.0	1.2	—
	Speedup	1.0	1.8	3.6	6.0	—
APO-A1 (92,000 atoms)	Time	32	18	9.3	4.6	2.4
	Speedup	1.0	1.8	3.4	7.0	13

Table 1: A table showing parallel scaling for NAMD 2 for two molecules. The tests were run on an SGI Origin2000.

*Further information about NAMD, and the program itself, can be found at `http://www.ks.uiuc.edu/Research/mdscope`.

Steered Molecular Dynamics of Biomolecules

Binding and unbinding of biomolecules are at the heart of almost all biologically important processes and are the target of many experimental investigations. In this respect steered molecular dynamics (SMD) serves as a complimentary tool to assist and navigate experimentalists in choosing protocols for their experimental studies. Biopolymers such as membranes, protein-membrane complexes, protein-DNA complexes and proteins bound to their ligands function in assemblies. The study of functional properties of assemblies often requires the atomic level description of binding and unbinding of constituent parts of the assembly, even when the function of each constituent is well known.

Several micromechanical manipulation techniques including atomic force microscopy (AFM), optical tweezers, and surface force apparatus experiments [6, 7, 8] have been applied to single molecules in small assemblies to investigate the unbinding processes between molecules. These techniques have also inspired the SMD approach.

SMD provides detailed atomic level descriptions of non-covalent interactions and allows one to observe processes which cannot be easily detected in experiments.

We applied this technique to investigate structural elements crucial for the association and dissociation of biological assemblies. We, then, attempted to relate these structural properties to the features of the energy landscape of the system [9]. The SMD technique has already contributed to studies of the dissociation of the avidin-biotin complex [10], the unbinding path of retinal from bacteriorhodopsin (bR, Isralewitz *et al.*, submitted to Biophysical Journal), and to the extraction of lipids from membranes by phospholipase A_2 (manuscript in preparation).

Avidin-Biotin (7,800 atoms)

The adhesion forces which bind the vitamin biotin to the protein avidin are known to be one of the strongest in biology [11] and have been directly measured [12, 13, 14].

We demonstrated that during the unbinding process the motion of biotin occurs in steps, breaking and forming successive networks of hydrogen bonds. Simulations showed that contacts of biotin with nonpolar residues (see Fig. 1a), as well as its interaction with one of the loops of avidin are crucial in the unbinding process. Our analysis of the dependence of the adhesion force on the speed of rupture suggested that computer simulations cannot be readily extrapolated to experimental time scales [10], indicating the need for further SMD method development currently in progress.

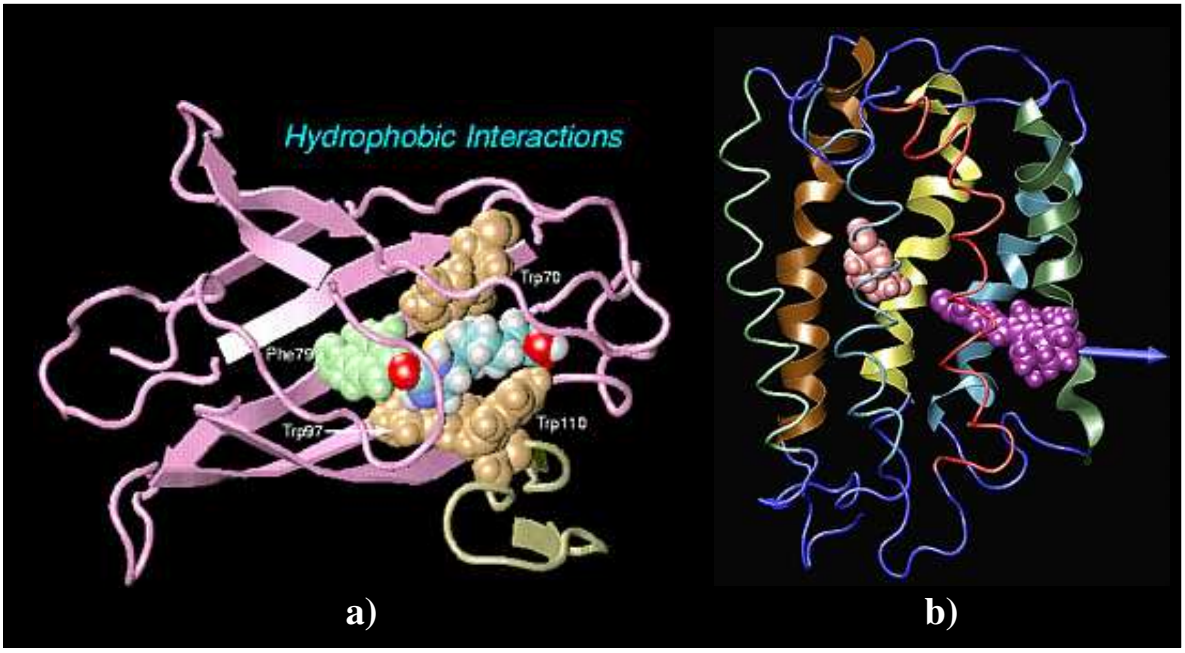

Figure 1:

a) Hydrophobic residues in the binding pocket of avidin monomer: Phe79, Trp70, Trp97 and Trp110 from adjacent monomer embrace biotin tightly from all sides making the binding pocket almost impenetrable for water. b) Retinal is being extracted from bacteriorhodopsin through the window between helices E and F.

Binding of Retinal to Bacteriorhodopsin (3,800 atoms)

The pathway of initial retinal entry [15, 16] during bR formation is poorly understood. Steered molecular dynamics allowed us to identify a path (see Fig. 1b) along which retinal binds to bacteriorhodopsin by means of extracting retinal from its bound position along a segmented unbinding path. At each segment the direction of the applied force was determined based on analysis of the protein structure.

Extraction of Lipids from Membranes (16,000 atoms)

Phospholipase A_2 (PLA_2) forms complexes with membrane surfaces and catalyzes the hydrolysis of phospholipids [17, 18, 19]. The catalysis is preceded by lipid extraction from the membrane. We used the SMD method to investigate this lipid extraction (see Fig. 2) by applying forces to the head group of a lipid such that the latter is pulled into the catalytic site of the enzyme.

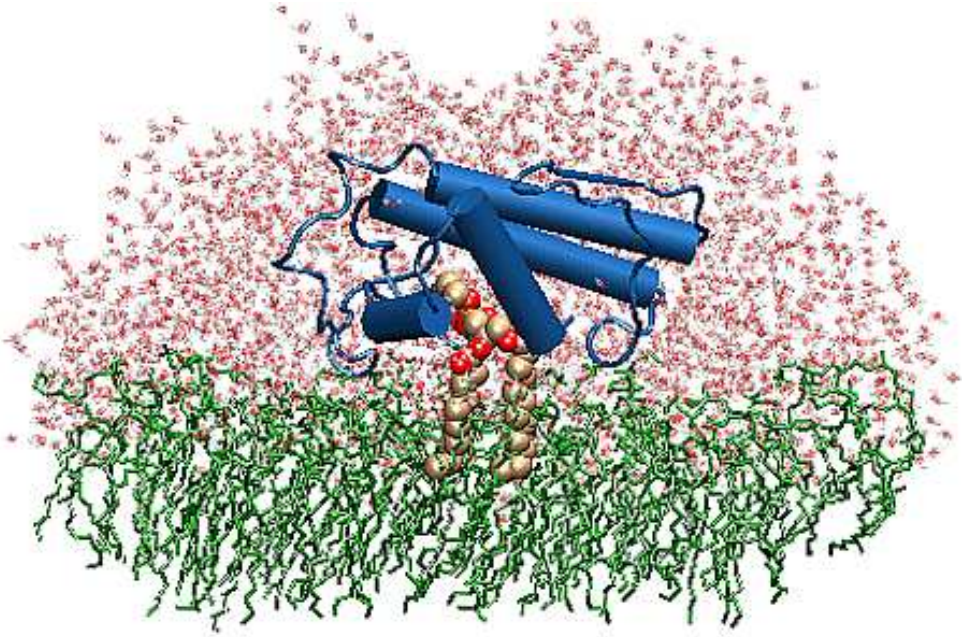

Figure 2:

Extraction of a lipid from the lipid monolayer by protein phospholipase A_2 in a water environment.

Cytochrome C Oxidase

Introduction

Cytochrome c oxidase (CcO) is the terminal enzyme of the respiratory chain in eukaryotes and most bacteria. It is located in the inner membrane of mitochondria and the cell membrane of prokaryotes, where it reduces molecular oxygen to water and, coupled to the redox reaction, pumps protons across the membrane [20, 21]. Defects in CcO have been shown to contribute to the pathogenesis of Alzheimer disease [22]. Recently, two crystal structures of CcO, one from the soil bacterium *Paracoccus denitrificans* [23], the other from bovine heart [24, 25], have been published, both of which were used in this study.

The catalytic site of CcO is a binuclear copper iron center formed by the heme a_3 and the copper Cu_B located in the enzymes subunit I (SU-I). In order to understand the function of this proton pump we have studied the pathways for transport of oxygen and protons to the binuclear center by predicting the distribution of water molecules in the protein and by molecular dynamics (MD) simulation of oxygen diffusion. Based on the results we have suggested a possible mechanism of proton pumping.

To make the simulation of oxygen diffusion computationally feasible, we employed a locally enhanced sampling (LES) technique [26, 27], which uses several copies of the diffusing oxygen molecule in the same simulation and reduces energy barriers for the oxygen molecules. Simulations were performed for both structures with the initial oxygen positions either at the approximate binding site between Cu_B and the heme a_3 iron or close to the entrance of the putative pathway. In all cases we observed the oxygen molecules to follow a similar pathway, leading from a hydrophobic cavity close to SU-III along a narrow channel lined with bulky hydrophobic residues to the binuclear center. This path is further supported by recent experiments [28], showing that the rate of O_2-binding is strongly affected by mutation of Val 279 at the beginning of the channel.

Proton transfer in proteins occurs typically through chains of hydrogen bonds. These chains often involve water molecules, which are known to form efficient "proton wires". Neither of the CcO structures presently available resolves bound water molecules. We attempted, therefore, to establish likely positions of bound water molecules using the program DOWSER [29] developed in the group of Jan Hermans (UNC) and subsequent refinement through MD.

The calculations predict about 130 water molecules within subunits I and II of each structure. The resulting distribution of water molecules for the *Paracoccus* structure can be seen in Figure 3. A large number of waters is predicted in the interface of subunits I and II and near the propionate groups of the hemes. Furthermore, the water molecules

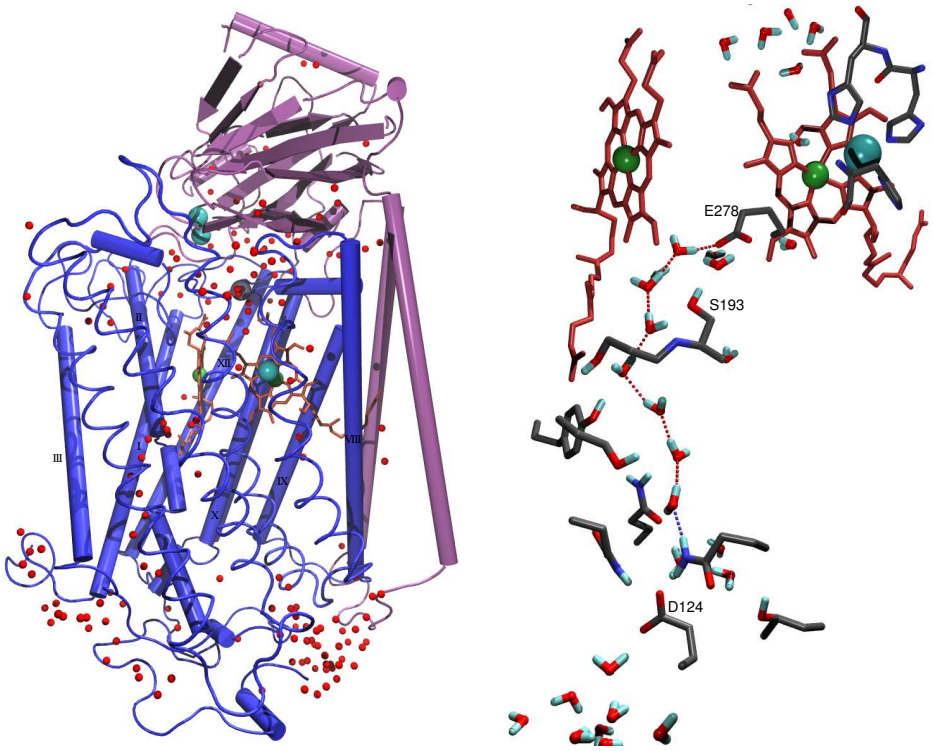

Figure 3: Water placement and proton channels in CcO. Left: Distribution of water molecules placed in the *Paracoccus* structure. Water oxygens are shown as small red spheres, large spheres are metals; Cu is presented in cyan, heme-Fe in green, and Mg in silver; subunits I and II are shown in blue and mauve. α-Helices are rendered as cylinders, except for SU-I helices IV to VII which are rendered as tubes to admit a better view into the structure. Right: a chain of hydrogen bonds (broken lines) involving seven water molecules connects Asp 124 to Glu 278.

so placed exhibit two possible pathways for taking up protons, one of which is shown in Figure 3. Both pathways are well supported by mutation experiments on key residues lining the path [30, 31, 32, 33, 34].

The proton pathway shown in Figure 3 ends at Glu 278 with no obvious continuation from there. We have proposed a proton pump mechanism in which the protonated glutamic acid side chain flips upwards to deliver its proton to a heme a_3 propionate group. MD simulations of the flipped side chain conformation show the formation of a water bridge to the propionate group to facilitate proton transfer from Glu 278. The large number of water molecules placed just above the propionate group makes it ideally suited as an acceptor of pumped protons. Subsequent transfer of "chemical" protons to the oxygen bound at the binuclear center would then provide the free energy to expel the pumped protons on the other side of the membrane.

Modeling of High Density Lipoproteins

Cholesterol is a small molecule which contributes to many processes essential for life. Most of the 100 g of cholesterol in the human body is found in cellular membranes, but it is also used to synthesize several steroid hormones, such as estrogen and testosterone, and is a precursor of vitamin D. The liver synthesizes about 2 g of new cholesterol each day, which is transported through the blood to body tissues by complexes of protein and lipid known as low density lipoproteins (LDL). Cholesterol is removed from cells and returned to the liver for recycling or excretion by the high density lipoproteins (HDL). Medical conditions such as atherosclerosis are influenced by the levels of LDL and HDL in the blood.

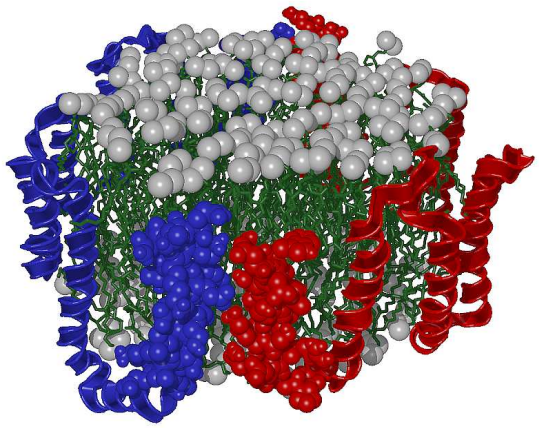

Figure 4: Predicted structure of rHDL particle. Two apoA-I molecules (light and medium gray) surround a bilayer of 160 POPC lipids (dark gray). The hydrophilic lipid head groups (top and bottom) are exposed to the solvent while the hydrophobic tails (center) are shielded by the amphipathic protein helices.

HDL particles are known to consist of phospholipids, 243 residue protein apolipoprotein A-I (apoA-I), and several minor proteins. The ability to create reconstituted HDL (rHDL) [35] has allowed the experimental study of particles with a defined composition. Typical nascent HDL particles are discoidal, consisting of two apoA-I proteins surrounding a circular patch of lipid bilayer. After collecting cholesterol, which is then esterized by the LCAT enzyme, an additional apoA-I molecule is incorporated and the particle transforms into a sphere with a core of cholesterol esters in a shell of lipid and apoA-I.

In order to study HDL via computer modeling, it is necessary to have an atomic resolution structure of apoA-I. Unfortunately, lipid-protein complexes are extremely difficult to crystallize and apoA-I is known to have different conformations in the states with bound and unbound lipids. Based on the regularity in the apoA-I sequence and experimental data on the structure of rHDL particles, we predicted the structure of an rHDL particle, as shown in Fig. 4.

The first 47 residues of apoA-I form a globular domain which does not bind to the lipids; our model does not deal with this part of the protein. The remaining residues are believed to form eight α-helices, the positions of which are clearly indicated in the sequence by 22 residue homologous repeats separated by "helix-breaking" proline residues. These helices are amphipathic, having one side which is hydrophobic and adheres to the lipid bilayer, and another which is hydrophilic and prefers the solvent. In this conformation, two apoA-I molecules can surround the exposed hydrophobic lipid tails on the edges of a bilayer disk containing the experimentally determined 160 POPC lipids. We have constructed such a particle (see Fig. 4) and tested its stability via simulated annealing [36].

Dynamics and Stability of Calmodulin in Solution

The dumbbell-shaped protein calmodulin belongs to a class of ubiquitous calcium-binding proteins of similar structure and function. Calcium-binding proteins regulate many important cellular processes such as smooth muscle contraction and sliding filament motion in skeletal and cardiac (heart) muscle. Our goal was to investigate the general structure–function relationship of this class of proteins. An understanding of the ways in which, for example, a cardiac muscle cell decodes calcium signals is naturally of interest to researchers interested in heart diseases.

Calmodulin utilizes the flexibility of its two domains to process and transduce a calcium signal in the cell. Upon activation by four calcium ions, hydrophobic patches are exposed on the surface of calmodulin's two lobes which allow the recognition of target peptide sequences. Calmodulin's two domains then wrap around a recognized α-helical peptide and, thereby, transduce the calcium signal to the target. Crystal and NMR structures of calmodulin in solution and in complex with target peptides are known [37, 38, 39]. We studied the dynamic aspects of calmodulin's flexibility and the time-dependent availability of its target-binding surfaces.

For this purpose a 3 ns simulation of the protein calmodulin in solution with Na^+ and Cl^- ions at physiological ionic strength was carried out. Earlier simulations by our collaborator were done only over relatively short time periods and in the absence of full solvent [40]. We placed the protein in a 44 Å radius sphere of water which resulted in a system of 33,000 atoms. The size of the simulated system and the length of the simulation time are unprecedented in computational studies of calcium binding proteins.

The long simulation time allowed us to study the dynamic processes which accompany calmodulin's solution state. The two calcium-binding domains of the dumbbell-shaped protein were found to reorient with respect to each other by approximately 60 ° within the first 1.5 ns simulation time, relaxing from packing forces present in the X-ray crystal structure [37]. The two domains then tumble independently in the water sphere, tethered by the central α-helix of the protein. The helix slowly unwinds, poised to assume an experimentally observed random-coil conformation [38]. This rearrangement brings the domains into a more favorable position for target peptide-binding by exposing the N-terminus binding patch (Fig. 5).

The 3 ns trajectory constitutes a benchmark for the study of physical properties of aqueous solutions near a protein. Earlier simulations of similarly sized solvated systems suffered from short simulation times which allowed one to sample only a small fraction of the total accessible sodium counterion configuration space [42]. The 3 ns trajectory permitted a near-complete sampling of the counterion distribution about the protein. We investigated the physical properties of water at the calmodulin-water interface. Recent studies suggest

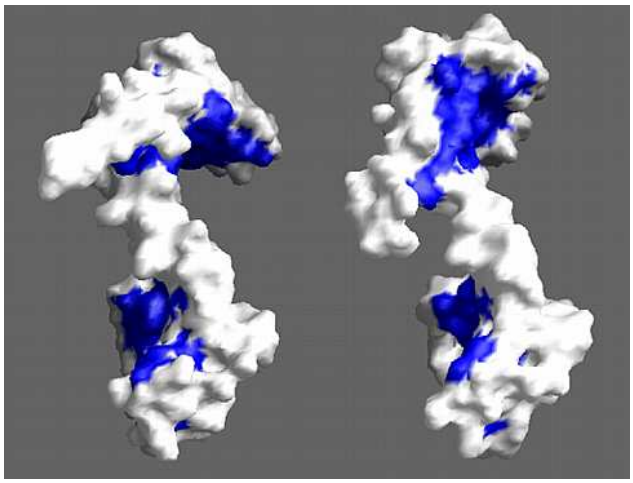

Figure 5:

Target peptide binding sites in calmodulin visualized by the program GRASP [41]. Left: Initial crystal structure [37]. Right: The structure after 3 ns simulation (averaged over the last 20 ps). Hydrophobic residues for which there exists NMR evidence for binding to myosin light chain kinase [39] are shown in blue.

a change in the mobility of water molecules near the surface of proteins [43]. Of special interest, in this respect, are calmodulin's hydrophobic target-peptide binding patches (Fig. 5). A new model of the hydrophobic effect suggests a reduced number of hydrogen bonds in the first solvation shell of hydrophobic compounds [44]. Consistent with this model, our simulations confirm that the mobility of water molecules is increased near calmodulin's hydrophobic patches relative to the otherwise polar surface of the protein.

Structure and Function Relationships of Cell-Motility Proteins

Adenosine triphosphate (ATP) is the source of metabolic energy which drives motor proteins. The energy is released after the proteins bind ATP and convert it to adenosine diphosphate (ADP) and phosphate. Our research was concerned with the fundamental structural processes which allow living organisms to move, namely, the mechanism of ATP-recognition and the response to ATP-hydrolysis. Our goal was to model the unbinding of phosphate after ATP hydrolysis in actin and to model nucleotide-dependent movements of kinesin.

Actin filaments are dynamic polymers whose ATP-driven assembly in the cell cytoplasm drives shape changes [45], cell locomotion [46] and chemotactic migration [47]. Actin filaments also participate in muscle contraction [48]. The mechanical properties of the filaments can be altered by actin-binding agents such as the toxin phalloidin from the mushroom *Amanita phalloides*. Phalloidin binding to actin has been shown to delay the release of inorganic phosphate after ATP hydrolysis [49].

In simulations of actin we observed the diffusion of water molecules into the buried nucleotide binding site along two distinct pathways (Fig. 6). Of particular interest is the "back door" diffusion pathway which we believe to be relevant for the dissociation of the phosphate after hydrolysis. Our hypothesis for phosphate release would explain the kinetics of actin-phalloidin interaction: phalloidin, whose position in the F-actin filament structure is known [50], would in our model block the exit of the "back door" pathway and, thus, delay the release of the phosphate.

In order to substantiate the "back door" hypothesis of actin phosphate dissociation we modeled the dissociation of this hydrolysis product by steered molecular dynamics (see also page 9). After hydrolysis, the phosphate in the form of $(HPO_4)^{2-}$ is tightly attached to the Ca^{2+} ion. Our results indicate that protonation of the phosphate to $(H_2PO_4)^-$ is the limiting factor in the phosphate release. This scenario of phosphate release is consistent with kinetic experiments [51]. The described work is the first computer simulation modeling the exchange of substrates in an ATPase. The methodology developed and the resulting structural prediction of the dissociation mechanism will benefit the research on other putative "back door" enzymes such as tryptophan synthase [52], acetylcholinesterase [53], the α-subunit of G-proteins [54], and the ATP-driven motor protein myosin [55].

Kinesin is the founding member of a superfamily of microtubule-based ATPase motors that perform force-generating tasks such as organelle transport and chromosome segregation [56]. The conformational differences between ADP and ATP-bound states and the structural basis for the movement of this motor is unknown. We predicted the structure of ATP-bound kinesin and identified conformational differences relative to the ADP-bound

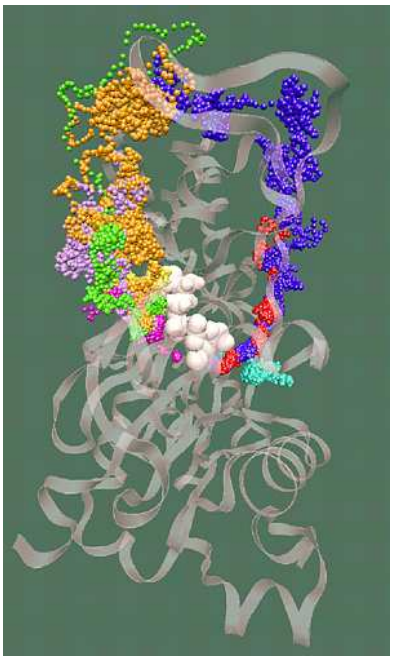

Figure 6:

Diffusion of waters molecules into the nucleotide binding site of actin visualized with the program `vmd` [2] (side view) ATP and the Mg^{2+}-ion are represented as white spheres in the center of the protein, which is rendered as a transparent ribbon. The color of the traces of the water oxygens codes for different simulation trajectories. This figure reveals two water diffusion pathways with the "back door" pathway on the right.

states which can be attributed to the force-producing ATP-hydrolysis. We searched for candidate structures in conformational space using a *simulated annealing* simulation protocol [57, 58, 59]. Movements in the crystal structure of ADP-kinesin were induced by placement of the ATP γ-phosphate and by inter-atomic distance constraints (*activated molecular dynamics* [60]). The constraints were based on mutagenesis results from the laboratory of Ron Vale (*pers. comm.*) and on comparisons with the known mechanism of nucleotide hydrolysis in G proteins, which are believed to be related to the ATP-driven motors [61]. Our results indicate the transfer of observable changes from the nucleotide pocket to the microtubule binding site. The activation of two 'γ-phosphate sensing' switches at Gly234 and Ser202 triggers a cascade of conformational changes in the kinesin motor domain. Nucleotide-dependent movements at kinesin's putative microtubule binding loops L8 and L12 correspond to a hinged rotation of the motor domain by 11° when bound to a microtubule. Recent electron microscopy experiments, which have shown that the orientation of a kinesin motor domain bound to a microtubule is nucleotide-dependent [62], are consistent with our results.

BTA UNIT: T

TITLE: Molecular Modelling: The Program NAMD

KEYWORDS: molecular dynamics, spatial decomposition, parallel, interactive

AXIS I: 9

AXIS II: 42 84

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% BRTP $: 25%

ABSTRACT: NAMD is the molecular dynamics simulation component of our molecular modelling environment, MDScope. It is novel in its field for its ground-up object-oriented parallel design implemented in C++. In the past year we have made progress in achieving all three major goals of the program: speed, accuracy, and modifiability. Sequential optimizations of the NAMD code improved both the speed and memory use of the program. In medium and large simulations, the short range non-bonded computation dominates execution time. The common method of performing these computations uses a pairlist database to keep track of which atom pairs require computation. Optimizing this database led to an overall decrease of NAMD memory use by seventy percent, and decreased execution times by sixty percent. All simulations exhibit a speed-accuracy tradeoff; greater accuracy requires a smaller stepsize and, thus, more simulation steps. Algorithmic improvements can allow to increase the stepsize without a loss of accuracy. The popular Verlet-I/r-RESPA *impulse* multiple time-stepping method requires the computation of long-range electrostatics every 4 fs. We have explained the mechanism for the loss of accuracy for longer stepsizes and have developed a *mollified* impulse method to overcome this barrier, pushing the achievable stepsize to 7 fs. Over the last year, we have been engaged in a complete rewrite of NAMD's computational core to increase modifiability and parallel efficiency. NAMD 2 uses several programming paradigms, including message driven execution and multi-threading, to separate the parallel communication code from the coding of mathematical algorithms, simplifying changes to either code. Finer decomposition of the force computations results in more independently-computable tasks for greater parallelization. Early evidence indicates that NAMD 2 will exhibit greater speed and better parallel speedups than NAMD 1.*

*URL: `http://www.ks.uiuc.edu/Research/namd/`

BTA UNIT: T,D

TITLE: Molecular Visualization: The Program VMD

KEYWORDS: molecular graphics, interactive visualization

AXIS I: 9

AXIS II: 42

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% BRTP $: 25%

ABSTRACT: VMD is the visualization component of MDScope, which is an integrated computational environment for structural biology.* In addition to supporting traditional molecular rendering styles and coloring methods, VMD also provides the biomedical community with several unique tools for molecular visualization. For instance, VMD is particularly useful for displaying simulation trajectories. These trajectories can be loaded from data files or captured in real time from ongoing molecular dynamics simulations. In the latter case, VMD can act as a graphical agent between user actions and subsequent molecular dynamics computation. This allows users to interact with simulated molecular systems through the application of steering forces, etc. To achieve such a high degree of interactivity, VMD experiments with several virtual reality input devices and methods. VMD has recently been modified to take advantage of database information available through the World Wide Web. The program can act as a helper application to web browsers and can automatically download molecular data in various formats from diverse locations such as the Protein Data Bank. Future versions of the program will enhance these data mining capabilities of VMD. VMD is designed to be a flexible and extensible program. It offers full support for the Tcl scripting language and is organized according to

*URL: `http://www.ks.uiuc.edu/Research/vmd/`

an object-oriented philosophy implemented in C++. The program is freely available to the molecular modelling community. It is provided with complete source code, extensive documentation, and precompiled binaries for SGIs, HPs, and Linux machines. Additional information on VMD may be found on the VMD web page.

BTA UNIT: T

TITLE: Steered Molecular Dynamics

KEYWORDS: ligand binding, energy landscape, avidin, biotin, bacteriorhodopsin, retinal, phospholipase

AXIS I: 2 9

AXIS II: 74h

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% BRTP $: 6%

ABSTRACT: We applied the steered molecular dynamics (SMD) method* to investigate the unbinding properties of three biomolecular aggregates. The unbinding of ligands from their substrates was induced by means of external harmonic forces. The simulations utilized the molecular dynamics software packages X-PLOR [63] and NAMD [3]. In our investigation of the avidin-biotin system, simulations induced the unbinding of biotin from avidin over a period of 40 ps to 500 ps. The simulations revealed a variety of unbinding pathways, the role of key residues contributing to adhesion as well as the spatial range over which avidin binds biotin. The SMD simulations were performed over a period of 0.2 ns, maneuvering the retinal from the binding pocket of bacteriorhodopsin in a series of successive force applications varying in direction. The simulations suggested that the window between bR helices E and F can be identified as an entry point for retinal as well as established that water plays a crucial role in the binding process. We investigate the extraction of phospholipid by the protein phospholipase A_2 for two complexes of the protein with a membrane surface, i.e., a tightly and a loosely bound complex. Our hypothesis is that the tightly bound complex facilitates the extraction of the phospholipid into the active site, while the loosely bound one does not [64]. We have demonstrated, using mathematical models, that computer simulations of ligand unbinding requires extremely strong forces. In this case the motion of the system proceeds far from the regime of natural dissociation. Nevertheless, the forces arising in SMD simulations can be used to reconstruct the potential energy surface governing the natural unbinding processes [9].

*URL: `http://www.ks.uiuc.edu/Research/METHOD/force_pull/`

BTA UNIT: T

TITLE: *Extended* Molecular Replacement

KEYWORDS: phase problem, x-ray crystallography, diffraction data, molecular replacement

AXIS I: 7a 9

AXIS II: 74h

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% BRTP $: 5%

ABSTRACT: The Resource has made a significant methodological advance in solving the well-known phase problem in x-ray crystallography. Typically, the phases are determined by cumbersome experimental techniques such as multiple isomorphous replacement, requiring crystallization of two or more heavy metal derivatives. We demonstrated that the conventional molecular replacement method can be extended through computational modeling to achieve a larger radius of convergence. Applying the method to x-ray diffraction data collected by our collaborator H. Michel, Frankfurt, Germany, we determined the structure of the light-harvesting complex II (LH-II) of *Rs. molischianum* [65, 66] using computer simulations to build a model structure from which the phase information can be deduced. The method promises, upon refinement and further testing, to expedite x-ray crystallographic macromolecular structure determination.*

*URL: `http://www.ks.uiuc.edu/Research/METHOD/mr/`

BTA UNIT: T

TITLE: Principal Component Analysis of Protein Motion

KEYWORDS: quasiharmonic analysis, collective motions, sampling problem

AXIS I: 9

AXIS II: 74

INVEST1: Willy Wriggers
DEGREE1: M.S.
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INVEST2: Manel Balsera
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% BRTP $: 2%

ABSTRACT: Reduced variable descriptions of protein dynamics attempt to extrapolate the results of MD simulations to millisecond time scales by analyzing the slowest collective motions. Principal component analysis,* also known as quasi-harmonic analysis, determines the slow collective motions using a preliminary atomic level detail simulation. Until recently, such analysis was considered a promising tool for reduced dynamics. However, we have shown [67] that principal component analysis is only useful when very long simulation time scales can be reached (microseconds appear to be required for most proteins). This negative result is most unfortunate but very important as it frees us and others to examine other directions which may prove to be fruitful. We continue to pursue the development of other reduced variable dynamics methods, such as torsion-angle dynamics.

*URL: `http://www.ks.uiuc.edu/Research/METHOD/long_time/`

BTA UNIT: T

TITLE: A Novel Algorithm to Investigate Protein Domain Movements

KEYWORDS: protein architecture, hinge-bending, actin

AXIS I: 9

AXIS II: 74h

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ABSTRACT: The activity of many proteins induces conformational transitions by hinge-bending, which involves the movement of relatively rigid parts of a protein about flexible joints. We have developed the *Hingefind* algorithm [68] to identify and visualize the movements of rigid domains about common hinges in proteins. In comparing two structures, the method partitions a protein into domains of preserved geometry. The algorithm uses two sets of atomic coordinates corresponding to the same protein in two conformations to find the "hinges." These different conformations may be obtained from crystallographic studies or, as we have recently demonstrated in the study of the protein actin, from computer simulations [68]. Using *Hingefind*, it is possible to construct reduced models of protein motions which consist of a set of hinge axes and rigid subunits. *Hingefind* may be of great utility in the quest for reduced variable protein dynamics and in the prediction of feasible binding modes for *induced fit*-docking of proteins.*

*URL: `http://www.ks.uiuc.edu/Research/METHOD/domain_mov`

BTA UNIT: C

TITLE: Modeling of the Bacterial Photosynthetic Unit

KEYWORDS: integral membrane protein, light harvesting complex, photosynthesis, tertiary structure, pigment organization

AXIS I: 7a 9

AXIS II: 74h

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% BRTP $: 5%

ABSTRACT: The photosynthetic unit (PSU) of purple bacteria is a nanometric assembly of light-harvesting complexes (LHs) which surround the so-called photosynthetic reaction center, involving hundreds of individual α-helical segments and thousands of bacteriochlorophylls and carotenoids. The PSU constitutes a molecular complex that is highly efficient in absorbing and in utilizing absorbed light quanta. To understand mechanisms for light absorption and utilization within the PSU, structural information of each component, as well as, information on the overall assembly of pigment-protein complexes is required. After successful determination of the crystal structure of light-harvesting complex II (LH-II)* of *Rs. molischianum*, reported previously, we have computationally modeled the atomic structure for the light-harvesting Complex I (LH-I) which directly surrounds the photosynthetic reaction center. Together with LH-IIs, LH-I yields a complete picture of pigment organization in the PSU. This accomplishment opens the door to both spectroscopic and theoretical studies of the pathways of excitation transfer and of the underlying transfer mechanisms in the bacterial photosynthetic membrane.

*URL: `http://www.ks.uiuc.edu/Research/bio_ener/LH_2/`

BTA UNIT: C

TITLE: Cytochrome C Oxidase

KEYWORDS: proton pumping, water placement, oxygen diffusion

AXIS I: 2 9 24

AXIS II: 30 46 74c 77 89

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% BRTP $: 7%

ABSTRACT: Cytochrome c oxidase (CcO), the terminal enzyme of the respiratory chain, is located in the inner membrane of mitochondria, where it reduces molecular oxygen to water and pumps protons across the membrane. Defects in CcO have been shown to contribute to the pathogenesis of Alzheimer disease [22]. Two crystal structures, one from the bacterium *Paracoccus denitrificans* [23], the other from bovine heart [24, 25] have been determined recently. Starting from the crystal structures we have studied the pathway along which the substrate oxygen diffuses to its binding site, as well as the pathways along which protons are transported. To determine how oxygen reaches the binuclear center, we simulated the diffusion of oxygen through the protein using molecular dynamics (MD). The computational cost of the calculation was reduced through the use of a locally enhanced sampling technique [26, 27], which allows one to obtain several oxygen trajectories from a single simulation and speeds up the dynamics by reducing energy barriers. Our simulations indicate a well-defined channel leading from the membrane-exposed surface close to subunit III of the protein to the binuclear center, which is consistent with recent mutation experiments [28]. Proton transfer through proteins often involves buried water molecules, which cannot be resolved in the available crystal structures. We have predicted water sites in CcO using the program DOWSER [29] and refined water positions using energy minimization and MD. The placed waters clearly define two possible pathways along which protons can be taken up that agree well with the

known mutation data [33, 30, 31, 32, 34]. Based on the water placement we have proposed a pumping mechanism in which protons are transferred to a heme propionate group via a side chain flip of Glu 278 (*Paracoccus* numbering), and have modeled the alternate conformation by MD.*

*URL: `http://www.ks.uiuc.edu/Research/bio_ener/cco/`

BTA UNIT: C

TITLE: Structure Prediction of Apolipoprotein A-I in rHDL Disks

KEYWORDS: HDL, reconstituted discoidal HDL, apolipoprotein A-I, apolipoprotein conformation, POPC, lipid bilayers, protein structure prediction, molecular dynamics simulations

AXIS I: 2 6 9

AXIS II: 74f,h 77

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% BRTP $: 3%

ABSTRACT: High density lipoproteins (HDL) circulate in the blood of vertebrates, transporting cholesterol from various body tissues to the liver for excretion or recycling. HDL particles are protein-lipid complexes of apolipoprotein A-I (apoA-I), several minor proteins, phospolipids, cholesterol, and cholesterol esters. Reconstituted HDL (rHDL), of defined compositions and sizes, have provided the best opportunities to experimentally study the structure-function relationships of apoA-I [35]. Nascent rHDL particles consist of a phospolipid bilayer disk surrounded by two apoA-I molecules. The amphipathic helices of apoA-I shield the hydophobic lipid tails, solubilizing the rHDL particle in water. Protein-lipid complexes are extremely difficult to crystallize and hence the structure of rHDL has not been observed experimentally. In order to study the system via computer simulation, we have been forced to construct a model of the tertiary structure of apoA-I in rHDL particles based on experimental evidence and sequence analysis [36]. In our model, we have neglected residues 1–47, which form a globular domain, and determined that the remaining residues 48–243 form eight amphipathic α-helices which, in a dimer, surround the membrane disk. We have tested our model via simulated annealing and found it to be stable. An upcoming crystal structure of a major N-terminal fragment of apoA-I which includes the globular domain will be compared to our model and incorporated in future simulations.

BTA UNIT: C

TITLE: Molecular Dynamics Study of Sequence Specific Protein–DNA Interactions

KEYWORDS: molecular dynamics, DNA, protein–DNA interaction, transcription regulation

AXIS I: 9

AXIS II: 74e,g,h

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INVEST2: Ann Nardulli
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% BRTP $: 6%

ABSTRACT: Estrogen Receptor (ER) is a member of the nuclear hormone receptor family of proteins that regulate gene expression by binding to specific sequences of DNA [69, 70]. The estrogen receptor protein plays a crucial role in the diagnosis and treatment of certain types of breast cancer, in a variety of biological processes including metabolism, stress response, and development of secondary sexual characteristics. To understand and explain the molecular basis of estrogen receptor DNA binding specificity, two simulations of the complex of a dimer of estrogen receptor DNA binding domains (ER-DBD), with DNA [71] have been conducted for a specific and a non-specific system. Each system consisted of approximately $36,500$ atoms including solvent and Na^+ ions for net charge neutrality. The molecular dynamics program NAMD [3], run on the Resource cluster, was used to compute two 100 ps trajectories, one for each system. The results of our study [72, 73] show that the binding specificity of the ER-DBD to different sequences of DNA is correlated to the positioning of the side–chains relative to the bases of the DNA, to the number and position of the water molecules found at the protein–DNA interface, and to the conformation of the DNA. The interaction of the receptor dimer with DNA results in a displacement or "jog" in the path of the DNA helical axis and underwound conformation of the DNA similar with the conformation of DNA in the nucleosome. We

suggest that binding of a receptor dimer to nucleosomal DNA changes the positioning of DNA on the nucleosome so that the symmetry axis of the hormone receptor dimer-DNA complex is aligned with the symmetry axis of the nucleosome.*

*URL:http://www.ks.uiuc.edu/Research/pro_DNA/ster_horm_rec/

BTA UNIT: C

TITLE: Molecular Dynamics Study of Architecture Specific Protein–DNA Interaction

KEYWORDS: molecular dynamics, DNA, protein–DNA interaction, transcription regulation

AXIS I: 9

AXIS II: 74g,h 77

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INVEST2: Mair Churchill
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% BRTP $: 6%

ABSTRACT: HMG-D is a member of the High Mobility Group 1 (HMG1) family of chromosomal proteins that participate in general modulation of chromatin structure and gene activity [74, 75, 76]. The proteins bind DNA and stabilize bent and supercoiled DNA structures, thus facilitating the formation of higher order nucleoprotein complexes, DNA packaging, or interactions with other proteins in chromatin [77, 78, 79, 80, 81]. In an attempt to predict the structure of the complex of HMG-D with DNA, the NMR model of free HMG-D [82] has been docked to three DNA fragments with experimentally determined structure. The trial structures were placed in an environment of water and ions. MD simulations of the systems allowed us to identify one of the three trial structures as being the most stable, best conserving the pre-engineered partial intercalation of Met13, and having the DNA geometry to which the other two complexes were converging. This system was chosen as our prediction of the structure of HMG-D-DNA complex. The structure of the protein and DNA in the predicted complex is similar to the experimental structures of HMG proteins LEF-1 and SRY complexed with DNA [83, 84]. Several differences in protein-DNA interactions between the model and the experimental structures provide a basis for explaning the known sequence-indifference of HMG-D binding to DNA. Wherever sequence-specific binding proteins, like SRY [84] and LEF-1 [83], have specific contacts with DNA bases, equivalent HMG-D residues interact with the DNA backbone or establish hydrophobic interactions in the DNA minor groove. Two novel partial

intercalations of hydrophobic residues, Leu9 and Val32, between the DNA bases are found in our model. A sequence comparison with other members of the HMG1 group [75] reveals that both intercalations may be characteristic for chromosomal HMG proteins, stabilizing non-sequence-specific protein-DNA complexes.*

*URL: `http://www.ks.uiuc.edu/Research/pro_DNA/hmgd/`

BTA UNIT: C

TITLE: Poliovirus Coat

KEYWORDS: poliovirus, molecular dynamics

AXIS I: 7b, 9

AXIS II: 74h

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INVEST2: James M. Hogle
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% BRTP $: 3%

ABSTRACT: Poliovirus is a small (diameter 300 Å), non-enveloped single-strand RNA virus. Its capsid proteins are of particular interest as they are expected to display multiple functional roles during different phases of the infectious life cycle of the virus. We are studying the effect of the so-called pocket factor in the poliovirus capsid protein VP1 β–barrel. We examined the structural changes in the VP1 β–barrel caused by deleting the sphingosine from the system. For this purpose, a pentamer(containing 5 protomers around a 5-fold axis of the icosahedral capsid), including a 60 Å sphere with capsid proteins and water was simulated. Two such structures were prepared: one with sphingosines in VP1 pockets and one without. The simulations revealed conformational changes around the VP1 pockets. A recent version of the program NAMD permitted the simulation of the whole poliovirus capsid of 587,200 atoms. Many properties involving system wide conformational change, for example the assembly and disassembly of the poliovirus capsid, require simulation of the complete capsid. The simulations demonstrated the possibility of studying large scale systems, and we expect to carry out detailed studies of the whole capsid as computing power increases and simulation methods improve.*

*URL: `http://www.ks.uiuc.edu/Research/virus/`

BTA UNIT: C

TITLE: Dynamics and Stability of Calmodulin in Solution

KEYWORDS: regulation, cell motility, muscle contraction, calcium, target peptide

AXIS I: 9 20

AXIS II: 42 74c,h 77

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INVEST2: Harel Weinstein
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% BRTP $: 2%

ABSTRACT: Calmodulin [37] belongs to a class of ubiquitous loop-helix-loop cation-binding proteins of similar structure and function. Calcium-binding proteins regulate many important cellular processes such as smooth muscle contraction and the cross-bridge motion in skeletal muscles. To characterize the dynamic behavior of the dumbbell-shaped protein in solution, we carried out molecular dynamics (MD) simulations of the Ca^{2+}-loaded structure. The crystal structure of calmodulin was placed in a solvent sphere of radius 44 Å, and 6 Cl^- and 22 Na^+ ions were included to neutralize the system and to model a 150 mM salt concentration. The total number of atoms was 32,867. During the 3 ns simulation the structure exhibited large conformational changes on the nanosecond time scale. The central α-helix, which was shown to unwind locally upon binding of calmodulin to target proteins, bent and unwound near residue Arg74. We interpret this behaviour as the initial step to a more extensive structural transition observed in the "flexible linker" region 74–82 of the central helix upon complex formation. The major structural change in the simulation was a reorientation of the two Ca-binding domains with respect to each other and a rearrangement of α-helices in the N-terminus domain which make the hydrophobic target peptide binding site more accessible. This structural rearrangement brings the domains to a more favorable position for target binding, poised to achieve the orientation observed in the calmodulin–myosin–light–chain–kinase complex [39]. An inhomogeneity of water mobility in the vicinity of the protein was

observed which can be attributed to the hydrophobic effect exerted by calmodulin's target peptide binding sites (manuscript in preparation).*

*URL: http://www.ks.uiuc.edu/Research/cell_motility/calmodulin/

BTA UNIT: C

TITLE: Structure–Function Relationship of Cell-Motility Proteins

KEYWORDS: actin, kinesin, ATPase, domain movement, power stroke, back door enzyme

AXIS I: 9 20

AXIS II: 42 74c,h 77

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DEPT1: Department of Physics
NONHOST1:

INVEST2: Jonathon Howard
DEGREE2: Ph.D.
DEPT2: Department of Physiology and Biophysics
NONHOST2: University of Washington

% BRTP $: 2%

ABSTRACT: The three-dimensional structures of a number of cell motility proteins were recently discovered and an understanding of the structure-function relationship for this class of proteins has now come within reach. Molecular dynamics simulation techniques were employed to investigate structure and function relationships in cell motility proteins at atomic resolution. Studies of the cytoskeletal ATPase actin, and the microtubule-based motor kinesin demonstrate the possibility to model protein domain movements and ligand-protein adhesion processes on the pico- to nanosecond timescale. Despite more than twenty years of software development and advancements in computer technology, conventional MD simulations have only very rarely led to insight into large-scale conformational changes of proteins. The reason for this "failure" is the limited simulation time, typically on the sub-nanosecond time scale, which in equilibrium situations does not allow one to sample slow motions of proteins in the accessible conformational space [67]. Non-equilibrium methods constitute one area where we have achieved progress in the modeling of large-amplitude motions. In cases where it is possible to focus on a specific mode or displacement path, mechanical perturbations are applied and the response of the system can be observed within a feasible simulation time. On this basis the Resource developed the technique to induce dissociation of a ligand from its binding pocket, by applying an external force (steered molecular dynamics method; see also above). We have

applied this method to study the unbinding reaction of phosphate after ATP hydrolyis in actin. A related method, *activated molecular dynamics* [60], was applied in the comparative modelling of nucleotide-dependent movements of the kinesin motor domain. Within the limited simulation time, sufficient sampling of these slow motions can thus be achieved under non-equilibrium conditions.*

*URL: `http://www.ks.uiuc.edu/Research/cell_motility/actin/`

	TECH RES & DEVEL (T)	COLLAB RES & SERVICE (C)	DISSEM & TRAINING (D)	TOTALS
NUMBER OF PUBLICATIONS	16	17	6*	39†
NUMBER OF SUBPROJECTS	6	8	1	15†
NUMBER OF INVESTIGATORS	16	17	2	35†
PERCENT OF BRTP FUNDS ALLOCATED	52%	35%	13%	100%
SERVICE FEES COLLECTED	0	0	0	0
OTHER FUNDS ($)	640,000	20,000 150,000	–	810,000

*Four of these were published only on our web-site.

†Investigators and subprojects classified to more than one BRTP unit were counted twice.

State or Country	Number of Investigators
IL	23
NY	1
Washington	1
MA	1
Germany	1

BRTP Unit T

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Balsera, Manel	University of Illinois (Oono, Yoshitsugu)	OTH	
Bhandarkar, Milind	University of Illinois (Kale, Laxmikant)	FED	NSF
Brunner, Robert	University of Illinois (Kale, Laxmikant)	FED	NIH
Dalke, Andrew	University of Illinois (Schulten, Klaus)	FED	NIH
Hu, Xiche	University of Illinois (Schulten, Klaus)	OTH	
Isralewitz, Barry	University of Illinois (Schulten, Klaus)	OTH	
Izaguirre, Jesus	University of Illinois (Skeel, Robert)	FED	NSF
Izrailev, Sergei	University of Illinois (Schulten, Klaus)	OTH	
Krawetz, Neal	University of Illinois (Schulten, Klaus)	FED	NSF
Michel, Hartmut	Max–Planck–Institute for Biophysics, Germany (Michel, Hartmut)	OTH	
Oono, Yoshitsugu	University of Illinois (Oono, Yoshitsugu)	OTH	
Phillips, Jim	University of Illinois (Schulten, Klaus)	FED	DOE
Shinozaki, Aritomo	University of Illinois (Schulten, Klaus)	FED	NIH
Stepaniants, Sergey	University of Illinois (Schulten, Klaus)	OTH	
Ulrich, Jeff	University of Illinois (Schulten, Klaus)	FED	NIH
Wriggers, Willy	University of Illinois (Schulten, Klaus)	OTH	

BRTP Unit C

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Balaeff, Alexander	University of Illinois (Schulten, Klaus)	OTH	
Bai, Linsen	University of Illinois (Schulten, Klaus)	OTH	
Churchill, Mair	University of Illinois (Churchill, Mair)	OTH	
Hofacker, Ivo	University of Illinois (Schulten, Klaus)	FED	NSF
Hogle, James	Harvard University (Hogle, James)	FED	NIH
Howard, Jonathan	University of Washington (Howard, Jonathan)	FED	NIH
Hu, Xiche	University of Illinois (Schulten, Klaus)	OTH	
Izrailev, Sergei	University of Illinois (Schulten, Klaus)	OTH	
Jonas, Ana	University of Illinois (Jonas, Ana)	OTH	
Kosztin, Dorina	University of Illinois (Schulten, Klaus)	OTH	
Lu, Hui	University of Illinois (Schulten, Klaus)	OTH	
Michel, Hartmut	Max–Planck–Institute for Biophysics, Germany (Michel, Hartmut)	OTH	
Nardulli, Ana	University of Illinois (Nardulli, Ana)	FED	NIH
Phillips, Jim	University of Illinois (Schulten, Klaus)	FED	DOE
Stepaniants, Sergey	University of Illinois (Schulten, Klaus)	OTH	

BRTP Unit C (cont.)

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Weinstein, Harel	Mount Sinai School of Medicine, CUNY (Weinstein, Harel)	OTH	
Wriggers, Willy	University of Illinois (Schulten, Klaus)	OTH	

BRTP Unit D

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Dalke, Andrew	University of Illinois (Schulten, Klaus)	FED	NIH
Ulrich, Jeff	University of Illinois (Schulten, Klaus)	FED	NIH

BTA unit: (T)

NUMBER PUBLISHED –
Books: 0 Papers: 3 Abstracts: 3

NUMBER IN PRESS OR SUBMITTED –
Books: 0 Papers: 9 Abstracts: 0

Books

PUBLISHED:

None

IN PRESS OR SUBMITTED:

None

Papers

PUBLISHED:

I. Kosztin and K. Schulten: "Boundary Integral Method for Stationary States of Two-Dimensional Quantum Systems", *Int. J. of Modern Phys. C*, **8**, 293–325 (1997).

B. J. Leimkuhler, S. Reich, and R. D. Skeel: "Integration methods for molecular dynamics", in J. P. Mesirov, K. Schulten, and D. W. Sumners, Eds., "Mathematical Approaches to Biomolecular Structure and Dynamics", Volume 82 of *IMA Volumes in Mathematics and its Applications*, pages 161–185. Springer-Verlag, 1996.

P. van der Smagt, F. Grön, and K. Schulten: "Analysis and control of a rubbertuator arm", *Biol. Cybernetics*, **75**, 433–440 (1996).

IN PRESS OR SUBMITTED:

M. Balsera, S. Stepaniants, S. Izrailev, Y. Oono, and K. Schulten: "Reconstructing Potential Energy Functions from Simulated Force-Induced Unbinding Processes", *Biophys. J.*, (1997), In press.

T. C. Bishop, R. D. Skeel, and K. Schulten: "Difficulties with Multiple Time Stepping and the Fast Multipole Algorithm in Molecular Dynamics", *J. Comp. Chem.*, In press.

A. Dalke and K. Schulten: "Using TCL for Molecular Visualization and Analysis", in "Proceedings of the Pacific Symposium on Biocomputing 97 on Interactive Molecular Visualization", 1997, In press.

B. Isralewitz, S. Izrailev, and K. Schulten: "Binding Pathway of Retinal to Bacterioopsin: A Prediction by Molecular Dynamics Simulations", *Biophys. J.*, Submitted.

W. Wriggers and K. Schulten: "Protein Domain Movements: Detection of Rigid Domains and Visualization of Hinges in Comparisons of Atomic Coordinates", *Proteins: Structure, Function, and Genetics*, (1997), In press.

M. Zeller, J. C. Phillips, A. Dalke, W. Humphrey, K. Schulten, R. Sharma, T. S. Huang, V. I. Pavlovic, Y. Zhao, Z. Lo, and S. Chu: "A Visual Computing Environment for Very Large Scale Biomolecular Modeling", in "Proceedings of the 1997 IEEE International Symposium on Computational Intelligence in Robotics and Automation (CIRA'97)". IEEE Computer Society Press, 1997, In press.

M. Zeller, R. Sharma, and K. Schulten: "Learning the Perceptual Control Manifold for Sensor-Based Robot Path Planning", in "Proceedings of the 1997 IEEE International Symposium on Computational Intelligence in Robotics and Automation (CIRA'97)". IEEE Computer Society Press, 1997, In press.

M. Zeller, R. Sharma, and K. Schulten: "Motion Planning of a Pneumatic Robot Using a Neural Network", *IEEE Control Systems Magazine*, **17**, 89–98 (1997).

M. Zeller, R. Sharma, and K. Schulten: "Vision-Based Robot Motion Planning Using a Topology Representing Neural Network", in J. Kalkkuhl, K. Hunt, R. Zbikowski, and A. Dzielinski, Eds., "Applications of Neural Adaptive Control Technology". World Scientific Publishing, 1997, In press.

Abstracts

Published:

B. Isralewitz, S. Izrailev, and K. Schulten: "Binding Pathway of Retinal to Bacterio-Opsin: A Prediction by Molecular Dynamics Simulations", *Biophysical Journal*, **72**(2), A208 (1997).

S. Izrailev, S. Stepaniants, M. Balsera, Y. Oono, and K. Schulten: "Molecular Dynamics Studies of Protein-Ligand Adhesion in the Avidin-Biotin Complex", *Biophysical Journal*, **72**(2), A106 (1997).

W. Wriggers and K. Schulten: "Opening Actin's Back Door by Simulated Micromanipulation", *Biophysical Journal*, **72**(2), A387 (1997).

In Press or Submitted:

None

BTA unit: (C)

NUMBER PUBLISHED –
Books: 0 Papers: 5 Abstracts: 0

NUMBER IN PRESS OR SUBMITTED –
Books: 0 Papers: 7 Abstracts: 3

Books

PUBLISHED:
None

IN PRESS OR SUBMITTED:
None

Papers

PUBLISHED:

T. C. Bishop, D. Kosztin, and K. Schulten: "How Hormone Receptor–DNA Binding Affects Nucleosomal DNA: The Role of Symmetry", *Biophys. J.*, **72**, 2056–2067 (1997).

X. Hu, T. Ritz, A. Damjanovic, and K. Schulten: "Pigment Organization and Transfer of Electronic Excitation in the Purple Bacteria", *J. Phys. Chem.*, **101**, 3854–3871 (1997).

X. Hu, D. Xu, K. Hamer, K. Schulten, J. Köpke, and H. Michel: "Prediction of the Structure of an Integral Membrane Protein–the Light-Harvesting Complex II of *Rhodospirillum molischianum*", in K. Merz and B. Roux, Eds., "Biological Membranes: A Molecular Perspective from Computation and Experiment", pages 503–533. Birkhäuser, Cambridge, MA, 1996.

W. Humphrey, E. Bamberg, and K. Schulten: "Photoproducts of Bacteriorhodopsin Mutants: A Molecular Dynamics Study", *Biophys. J.*, **72**, 1347–1356 (1997).

S. Izrailev, S. Stepaniants, M. Balsera, Y. Oono, and K. Schulten: "Molecular Dynamics Study of Unbinding of the Avidin-Biotin Complex", *Biophys. J.*, **72**, 1568–1581 (1997).

IN PRESS OR SUBMITTED:

I. Hofacker and K. Schulten: "Oxygen and Proton Pathways in Cytochrome c Oxidase", *Chemistry and Biology*, Submitted.

X. Hu and K. Schulten: "How Nature Harvests Sunlight", *Physics Today*, (1997), In press.

W. Humphrey, H. Lu, I. Logunov, H. J. Werner, and K. Schulten: "Three Electronic State Model of the Primary Phototransformation of Bacteriorhodopsin", *Proc. Natl. Acad. Sci. USA*, Submitted.

D. Kosztin, T. C. Bishop, and K. Schulten: "Binding of the Estrogen Receptor to DNA: The Role of Waters", *Biophys. J.*, In press.

J. C. Phillips, W. Wriggers, Z. Li, A. Jonas, and K. Schulten: "Predicting the structure of apolipoprotein A-I in reconstituted high density lipoprotein disks", *Biophys. J.*, Submitted.

S. Tzonev, J. Malpeli, and K. Schulten: "A three-dimensional model of the morphogenesis of the Rhesus lateral geniculate nucleus", *Journal of computational neuroscience*, Submitted.

W. Wriggers and K. Schulten: "Stability and Dynamics of G-actin: Back Door Water Diffusion and Behavior of a subdomain 3/4 loop", *Biophys. J.*, (1997), In press.

Abstracts

PUBLISHED:

A. Balaeff, M. Churchill, and K. Schulten: "Structure of the complex of HMG-D protein with DNA as predicted by means of molecular modelling", *Biophysical Journal*, **72**(2), A107 (1997).

W. Humphrey, H. Lu, I. Logunov, H-J. Werner, and K. Schulten: "Three Electronic State Model of the Primary Phototransformation of Bacteriorhodopsin", *Biophysical Journal*, **72**(2), A208 (1997).

W. Wriggers and K. Schulten: "Atomic Resolution Model of the Kinesin Power Stroke", *Biophysical Journal*, **72**(2), A61 (1997).

IN PRESS OR SUBMITTED:

None

BTA unit: (D)

NUMBER PUBLISHED –
Books: 0 Papers: 2+4* Abstracts: 0

NUMBER IN PRESS OR SUBMITTED –
Books: 0 Papers: 0 Abstracts: 0

Books

PUBLISHED:

None

IN PRESS OR SUBMITTED:

None

Papers

PUBLISHED:

W. F. Humphrey, A. Dalke, and K. Schulten: "VMD – Visual Molecular Dynamics", *J. Mol. Graphics*, **14**, 33–38 (1996).

I. Kosztin, B. Faber, and K. Schulten: "Introduction to the Diffusion Monte Carlo Method", *Am. J. of Phys.*, **64**, 633–644 (1996).

IN PRESS OR SUBMITTED:

None

Abstracts

PUBLISHED:

None

IN PRESS OR SUBMITTED:

None

WEB DOCUMENTS:

VMD User Guide (Version 1.0)
URL: `http://www.ks.uiuc.edu/Research/vmd/ug/`

VMD Programmer Guide (Version 1.0)
URL: `http://www.ks.uiuc.edu/Research/vmd/pg/`

NAMD User Guide (Version 1.0)
URL: `http://www.ks.uiuc.edu/Research/namd/ug/`

NAMD Programmer Guide (Version 1.0)
URL: `http://www.ks.uiuc.ed/Research/namd/pg/`

*four of these published on our web-site

Advisory committee

The Advisory Board has made visits to the Resource in each of the past three years. Following is the most recent report. The unequivocal impact of the Board's advice and recommendations concerning our research and development activities has turned the yearly visit into a notable event on the Resource calendar. Board members' busy schedules have led to some changes in membership. We believe, however, that the current members' well established expertise and knowledge are as relevant to the Resource, and their contribution is invaluable.

Name	Institution
Bernie Alder	Lawrence Livermore Lab.
Peter Arzberger	Office of Advanced Scientific Computing UCSD
William Gear	President NEC Research Inst. Inc
Karl Hess	UIUC, Computer and Electrical Engineering
Christof von der Malsburg	USC, Computational Vision Lab.
Attila Szabo	National Institutes of Health Lab. of Chemical Physics

Table 2: Resource Advisory Board

Advisory Committee Report (November 15, 1996)

Introduction The committee, has visited the NIH Resource at the Beckman Institute for a full day, received a presentation by the group (see accompanying program, Appendix 1), saw demonstrations, and has led various discussions with group members and administrators. We here report on our impressions and recommendations, with the goal of helping the Resource to achieve even greater impact on the biomedical community.

In recent years, the Resource has concentrated all its efforts on the development of computational tools and original research in the field of biomolecular dynamics. We share the vision of the Resource that biomolecular computing is a field that will play an increasingly important role in Molecular Biology and Bio-Medicine and that there is an urgent need to expand the scope, power and availability of its methods. Ideally, they will complement the techniques of the future molecular laboratory as yet another range of research tools.

Modeling of biological molecules faces formidable computer problems. Let it be said at the outset that the facility has gotten superb results already on systems as large as 30,000 atoms with excellent graphic displays which have led to new physical insights into biological processes. It is now becoming feasible and necessary to understand higher order organizations that form molecular assemblages, e.g., hormone-receptor complexes,

or molecules within their lipid or aqueous environment. The flood of genetic information to be expected over the coming decade will dramatically step up the demand for tools for theoretical analysis. Thus, more efficient tools for obtaining protein tertiary structures from X-ray data could speed progress tremendously.

Research The value and potential of the Resource lies in its double motivation to seriously invest in tool development while at the same time doing front-line research. The latter is absolutely necessary to guarantee the quality, relevance and authority of the tools developed. The Resource has presented an impressive wealth of first-rate research results. Many of these are the result of intensive collaborations with experimental groups that furnish the necessary data. Thus, the Resource has developed a new approach to the missing-phase problem of X-ray diffraction analysis of molecular structure, an approach they call "*ab initio* molecular replacement." As a demonstration of the method the group has worked out the structure of the light-harvesting complex LH-II, in collaboration with H. Michel, Frankfurt. An important line of research concerns a regulatory protein-DNA complex in a water bath (up to 36,000 Atoms). This work may turn out to be of great importance for issues of gene regulation. Another piece of work concerns the activation of the enzyme phospholipase A2 upon complexing with lipid membranes. In collaboration with Malpeli, UIUC, the group has continued earlier work on the ontogenesis of the visual system. Although this work is not of the molecular dynamics type, it illustrates the group's strengths and breadth in terms of interdisciplinary integration and high-power biological computation. We feel that the Resource has a very impressive record in terms of scientific achievements and publications, even if judged as a pure research group.

Computing Equipment The NIH-funded computational group at the University of Illinois at Urbana-Champaign made the right choice of architecture for a biomolecular modeling resource when it chose to use a cluster of workstations, soon to be replaced by clusters of PC's. This will also be the architecture of the next generation of supercomputers to be built by IBM and Cray and ordered by Livermore and Los Alamos. This structure is well suited to the type of parallelism that is found in molecular modeling – a computational problem that is not well served by either the vector computing of conventional supercomputers or the lock-step processing of SIMD-type parallel computers.

Software Design Even with the right choice of computer system, challenging problems in software organization as well as in improving the underlying numerical algorithms remained, and the group has made an excellent start on these problems. It is particularly notable that the group includes two computer scientists with expertise in the area most critical to the computational part of this work – the organization of a complex, parallel

code in a way such that it can easily be modified and extended in the future. The code has apparently been designed in a structured, modular approach using a modern object-oriented paradigm. It appears that these people have made valuable contributions to the project, which we recommend they document as concretely and quantitatively as possible for the purpose of the coming site visit.

Computational Methods By developing and testing new algorithms potentially huge gains can be made. This is also in the hands of computer scientists with the help of a few outside collaborators. The help of a knowledgeable computational physicist/chemist would be most useful in selecting the most suitable methods and the addition of Todd Martinez as a fourth principal investigator is a most valuable step. Opportunities for improvements are new integrators, for example the multiple time procedure Respa as well as faster electrostatic summation methods. Such developments take time to carry out, but must be pursued, since they are of as much potential benefit as better hardware.

This still leaves out other improvements such as getting better force fields through quantum Monte Carlo calculations with good pseudo-potentials, or the idea of embedding the biomolecule into a continuum to reduce the number of degrees of freedom that one has to deal with. The Resource has focussed recently mainly on setting up a framework for the new parallel molecular dynamics program NAMD, now in versions 1.x and 2.0 and it is advisable that the future focus will be on strengthening the algorithmic area.

Technical Service The resource has developed and disseminated a package of software under the name MDScope, which includes a visualization package (VMD), a molecular dynamics package (NAMD), a communications package (MDComm), and a software engineering tools component (MDTools). Making these tools available to the community, providing the community with searchable manuals, and offering training, are very valuable services.

The Resource has taken earlier advice of the Advisory Committee and conducted a survey of the use of these tools. This is a significant first step in involving the community in the development of this package. Other activities of involving the community include the collaborative projects. In virtually every case presented at our visit the software was used to address a specific problem worked on jointly by the collaborators and a member of the Resource. This interaction between experimentalists and theoreticians is critical for the mission of this resource. In addition, the Resource makes available the computational facilities to outside groups.

The Resource's plans for the future involve continued development of searchable software manuals and a help-line for the software. In addition, the Resource will be building its

visitor program to catch a wider section of the community in a more systematic fashion (for use of the Resource as well as training and dissemination).

We recommend to

- continue the documentation of use of computational resources (who is using it, how one gets access, etc.) at the present level;
- administer the survey regularly and adjust according to needs;
- consider an MDScope users/advisory committee. We understand there is such a group locally - expand it.

General Services The Resource has been active in its organization of seminars (locally), meetings and conferences. These activities will continue and will grow naturally. In addition, the group did document the use of the 3D facilities.

Recommendation: It is very difficult to develop and maintain a visualization lab that is considered unique; the trend in visualization is being driven by the PC market. The aim of the Resource to pioneer a widely accessible visualization resource through their program VMD should definitely be pursued; the Resource should realize the plan to port VMD, through Open GL, to many platforms as soon as possible.

Training The Resource provides several mechanisms for training: workshops, visitors, classes in the 3D facility, and the involvement of graduate and undergraduate students in the Resource. One aspect of the training of graduate and undergraduate students that is quite compelling is the multidisciplinary origin of the members of the Resource, coming from physics, chemistry, biophysics, and computer science. These types of interactions at this stage of the students' careers is critical to the challenges we see facing researchers in the future (the exciting science is going to be at the interface of traditional disciplines). The Resource is planning to continue and expand training workshops for MDScope and its individual components. This will be essential. In addition, the Resource will be expanding its visitor program to provide more training.

We recommend to involve other resources (e.g. supercomputer centers) during the development of tools, to ensure training for the biomedical community on a broad variety of resources and to leverage other training activities.

Dissemination This Resource has recognized early on the power of the web to disseminate information. It has developed a very impressive web site that reflects the dynamic and active nature of the members of the Resource. Furthermore, the energy of this group is noted in the number of publications.

Recommendation: All of the major developments from the group would have an obvious dissemination avenue if MDScope was adopted by a large portion of the community.

Dissemination

The Resource has made a conscientious attempt in the past grant period to fully benefit from the wide array of communication and dissemination tools available today. All software manuals and documentation are posted on our web site, as well as images and results of recent work (`http://www.ks.uiuc.edu/`); research and development accomplishments are published in professional journals and are posted on the web; lectures and talks describing the Resource activities are given all over the world; various documents such as reports and brochures, are periodically mailed to colleagues, prospective members, and federal offices, and are posted on the web (`http://www.ks.uiuc.edu/Publications/Reports/`). Videotapes and slides are regularly made in response to requests from funding agencies, collaborative groups and local administrators. The staff continuously reports key findings and systematically disseminates new knowledge produced by the Resource.

- The Resource's web site (`http://www.ks.uiuc.edu/`) represents the group's scientific efforts to the outside world. The external web site is accessible to all Internet users. The site includes both scientific and administrative information such as software and hardware available, current research projects, main research accomplishments, image gallery, publication list, the people in the group, as well as our seminar series, special events organized by the Resource, job announcements, training and learning opportunities, and more. A search of the web indicates that there are over 200 links to our web pages.

- The principal instrument for the dissemination of software tools and information on prototype modeling projects and related activities is the Resource's web site (`http://www.ks.uiuc.edu/`). The three components of MDScope, NAMD, VMD and MDComm, are available in source form without charge or license requirements from the Resource's anonymous ftp site at `ftp.ks.uiuc.edu`. VMD and NAMD are accompanied by a User's Guide for general users, and a Programmer's Guide for those who want to modify the programs. Additional information is available on the MDScope web pages, at `http://www.ks.uiuc.edu/Research/mdscope/`. The original versions of VMD and NAMD were publicly announced on July 1, 1995 to the relevant newsgroups and mailing lists. To date, there have been over 1,300 downloads of VMD and over 600 of NAMD, though that does not indicate the number of current users. We provide user support through email. Over the last 14 months there has been 293 queries from 137 different users. The Resource is dedicated to the development of software which can be freely used and modified by other researchers. By releasing readily extensible software for general use, others can concentrate on adding the specific features needed on top of a well-developed base, instead of having to re-implement the same features. In this way, third-party

users can make their own modifications as appropriate and even contribute their own results back to the MDScope effort. To aid other development, we will continue to distribute MDScope and its components without charge along with accompanying documented source code and manuals.

- Online newsgroups have been a major channel for the dissemination of MDScope. Newsgroups used for dissemination include:
  - bionet.molbio.proteins
  - bionet.molec-model
  - bionet.biology.computational
  - comp.sys.sgi.announce (VMD only)
  - bionet.announce
  - bionet.software
  - comp.lang.tcl.announce (VMD only)

  A report on the package was published in the PDB newsletter (July 1996), and another was published in the NCSA Access Magazine (fall, 1996). NAMD was announced on the computational chemistry mailing list.

- The images in the Resource web gallery illustrate the main lines of the Resource activities (`http://www.ks.uiuc.edu/Overview/gallery/`). The 'collections' in the gallery are continuously updated.

- Over the past year we have added a movie gallery that is continuously updated (`http://www.ks.uiuc.edu/Overview/movie_gallery/`).

- During the past year the Resource has published and/or submitted 35 scientific papers (list on pages 48-53). The Resource also makes its publications available as preprints and reprints in the form of Technical Reports. The manuscripts are maintained in a data base accessible to Internet users and are made available upon request (`http://www.ks.uiuc.edu/Publications/Papers/`).

- The Resource maintains a slide library containing images representative of the group research efforts. The slides are used for presentations by Resource staff and by university and federal administrators. The slides also serve as a source of visual information in discussions with collaborators and other scientists.

- The videotapes produced by the Resource staff are instrumental for succinct multimedia depiction of the work performed at the Resource. They are typically made in response to requests from our funding agencies and for special events.

- The Resource has established a tradition of a yearly Open House. The event attracts many on-campus visitors, both students and faculty, and generates increased interest in our research and development efforts.

- The Resource has designed a new VMD brochure that offers an effective vehicle to introduce the software to the wider community, and revised the group brochure (Appendix 2 and 3).

- To increase the effectiveness of our dissemination efforts we organized a workshop for the Resource members, focusing on the art of presentation and scientific writing. The workshop proved to be a useful and worthwhile experience and similar training opportunities are planned for the future (Appendix 4).

The PI has presented the following lectures during the past year:

- May 31, 1996, Juelich Research Center, Department of Solid State Physics; Lecture: *Bakterien kennen Quantenmechanik: Optimierung von Energie-, Elektronen- und Protonenleitung in bioenergetischen Proteinen*

- June 8, 1996, University of Bochum, Germany, Birthday Colloquium of Professor von Seelen; Lecture: *Was sieht mein Homunculus wenn ich sehe? Zur Geometrie von Gehirnkarten*

- June 17, 1996, University of Frankfurt, Department of Physics; Lecture: *Beauty in the Eye and the Brain of the Beholder - Morphogenesis of the Retinal-LGN-Cortical Pathway*

- June 23, 1996, Retinal Conference, Tel Aviv University, School of Chemistry; Lecture: *Reduced Descriptions of Protein Dynamics*

- August 1996, ACS meeting, Orlando, FL; Lecture: *Biomolecular Assemblies: The New Frontier in Modelling*

- September 5, 1996, University of Illinois, Department of Physics Colloquium, Urbana, IL; Lecture: *How Nature Harvests Sunlight: the Bacteria's Tale*

- October 7, 1996, ECMBM meeting, Heidelberg, Germany; Lecture: *Very Large Scale Molecular Dynamics Simulations: Achievements and Challenges*

- October 15, 1996, Symposium on Computer Modelling of Materials, University of Pennsylvania, Philadelphia, PA; Lecture: *Biopolymer Aggregates and Biology on the Scale 1-1000 Nanometers*

- October 1996, International Symposium on Molecular Dynamics of Biomembranes, The University of North Carolina at Chapel Hill; Lecture: *Nanoscale Organization and Function of a Bioenergetic Membrane*

- November 19, 1996, University of California-San Diego; Lecture: *How Nature Harvests Sunlight: the Bacteria's Tale*

- December 1996, 25th Anniversary Symposium on Molecular Mechanisms in Chemistry and Biology, Goettingen, Germany; Lecture: *Energy migration, electron and proton transfer - Three tales from Goettingen still being told*

- January 1997, 32nd Winter Seminar, Molecular Biology and Biophysical Chemistry of the Cell, Klosters, Switzerland; Lecture: *Light Harvesting physics: Structure and function of a large protein aggregate*

- March 1997, 37th Annual Sanibel Symposia on Theoretical and Computational Chemistry, Condensed Matter Physics and Biology, St. Augustine, Florida; Lecture: *Chromophore Organization and Transfer of Electronic Excitation in the Photosynthetic Unit of Purple Bacteria*

- March 16-20, 1997, U.S. Japan Joint Seminar on the "Structural Basis of Information Transfer and energy Transduction in Rhodopsins," Kyoto University, Kyoto, Japan; Lecture: *Investigations of the mechanism of bacteriorhodopsin by molecular dynamics and quantum chemistry*

- March 21, 1997, One day seminar, Nagoya University, Nagoya, Japan; Lecture: *How Nature Harvests Sunlight*

- April 8, 1997, Physical Science Seminar, University of California at Irvine; Lecture: *Chromophore Organization and Transfer of Electronic Excitation in the Photosynthetic Unit of Purple Bacteria*

- April 26, 1997, CIAR Program on the Science of Soft Surfaces and Interfaces, Vancouver Canada; Lecture: *Molecular Dynamics Simulations of Proteins and Lipids*

- May 2, 1997, Mount Sinai, New York; Lecture: *Investigations of the Mechanism of Bacteriorhodopsin by Molecular Dynamics and Quantum Chemistry*

- May 9, 1997, Molecular Biophysics: At the Interface Between Physics and Biology Theoretical Physics Institute, Minneapolis, MN; Lecture: *Chromophore Organization and Transfer of Electronic Excitation in the Photosynthetic Unit of Purple Bacteria*

- May 21-24, 1997, 2nd International Symposium on Algorithms for Macromolecular Modeling, Berlin, Germany; Lecture: *Modelling Very Large Molecular Aggregates*

- June 4, 1997, Theoretical Chemistry in Biology: From Molecular Structure to Functional Mechanisms, Savannah, Georgia; Lecture: *Chromophore Organization and Transfer of Electronic Excitation in the Photosynthetic Unit of Purple Bacteria*

During the past year the PI served on the following committees and editorial boards:

- Appointments and Promotions Committee, Physics Department, UIUC
- Biotechnology Center Advisory Committee Member, UIUC
- Department of Physics Qualifying Examination Committee, UIUC, Fall 1996
- Research Resource Committee, UNC, February 26, 1997
- NIH Special Study Section, Rockville, MD, April 3, 1997
- Chair, Ad Hoc Subcommittee to Evaluate ECE 458, UIUC, April 1997
- Reviewer for: National Institutes of Health and National Science Foundation, Journal of Molecular Biology, Biochemistry, J. Physical Chemistry, J. Chem. Phys., Chemical Physics Letters, Biological Cybernetics, IEEE Transactions on Systems, Man and Cybernetics, Journal of Computational Chemistry, Biophysical Journal, The Physical Review, Physical Review Lett., Science
- Co-Editor for: Physics of Neural Networks (Springer Series)

During the past year research personnel of the Resource have participated and/or presented contributions at the following meetings and institutions:

- Wayne State University seminar "Structures of Bacterial Light-harvesting Complexes and Dynamics of Energy Transfer" (X. Hu)
- Seminar at NIH, 1996. (S. Stepaniants)
- Beyond Protein Structure, The Pfizer Inc.-Beckman Institute Symposium, Urbana, IL (X. Hu, B. Humphrey, T. Bishop, S. Stepaniants, A. Balaeff, S. Izrailev, W. Wriggers)
- Gordon Research Conference, New London, NH (W. Wriggers)
- Illinois Summer Software School/Adv C++ Programming, Urbana, IL (A. Shinozaki, A. Dalke)
- KDD'96 Conference, Portland, Oregon (I. Hofacker)

- ICPR Conference, Vienna, Austria, (M. Zeller)
- Daimler-Benz Workshop, Berlin, Germany (M. Zeller)
- American Chemical Society Conference, Orlando, Florida (X. Hu)
- WCNN Conference, San Diego, CA (M. Zeller)
- GCAG-96 Retreat, New York City (J. Phillips, D. Kosztin, X. Hu, R. Brunner, A. Balaeff, H. Lu, S. Izrailev, A. Zhou, B. Izralewitz, R. Skeel, K. Schulten, L. Kale, S. Stepaniants)
- Workshop on Innovative Time Integrators, Amsterdam, The Netherlands (R. Skeel)
- Fall Symposium, Biomolecular Imaging, Canada (W. Wriggers)
- Mount Sinai School of Medicine, CUNY (W. Wriggers)
- Rice University (X. Hu)
- Seminar at Boston University (S. Stepaniants, S. Izrailev)
- Seminar at Northeastern University (S. Stepaniants)
- Molecular Structure: Dynamics, Geometry and Topology seminar, sponsored by the Inst. for Math. and Applics., Minneapolis, MN (R. Skeel)
- Molecular Biology and Biophysical Chemistry of the Cell, Klosters, Switzerland (I. Hofacker)
- MPI für Biophysik Chemie, Frankfurt, Germany (I. Hofacker)
- Pacific Symposia on Biocomputing, Kapalua, HI; UCSF/CGL and Interactive Simulations, inc., San Francisco, CA (A. Dalke)
- BPS meeting, New Orleans, LA (W. Wriggers, D. Kosztin, A. Balaeff, H. Lu, S. Izrailev, B. Isralewitz, S. Stepaniants, X. Hu)
- SIAM Conf. Parallel Proc. for Science Computing, Minneapolis, MN (R. Skeel, J. Izaguirre)
- UIUC Photosynthesis Community Retreat, Allerton, IL (A. Damjanovic, T. Ritz)
- Conference on Molecular Interactions of Actin, Maui, Hawaii (W. Wriggers)
- Second International Symposium Algorithms for Macromolecular Modelling, Berlin, Germany (R. Skeel, J. Phillips)
- NSF-CBMS Conference Numerical Analysis of Hamiltonian Dif Eqs, Golden, Colorado (R. Skeel)

Service

The scope of our services have been determined to a large extent by the development stage of the Resource. Accordingly, in the last two years of the grant period there has been a marked expansion in the services provided by the Resource. The services we offer may be classified into two broad categories: *technological services* designed to provide the scientific community with easy access to the Resource's software and hardware technology, and *general services* which focus on creating new collaborations, sharing the knowledge and expertise produced by existing collaborations, and ongoing application projects with other biomedical scientists.

Technological Services

- The release of VMD and NAMD was announced on July 1, 1995 . MDComm was released May 1, 1996. There have been over 2663 downloads of VMD and 981 of NAMD to date.

- The VMD and NAMD manuals have been made available on our web site, and are searchable. We will add extra documents describing how to use specific aspects of the software, such as a manual for using VMD to produce high-quality images. In the past two months the VMD page has been accessed 11,259 times, and the NAMD page 1,132 times.

- The MDScope web page page is located at

  `http://www.ks.uiuc.edu/Research/mdscope/`

  In a recent search of the World Wide Web, we found nearly 150 sites containing direct references to VMD, and over 50 to NAMD. Among these sites are the National HPCC Software Exchange, the Brookhaven PDB page, NIH Molecular Modeling page, and the European Bioinformatics Institute BioCatalog.

- The MDScope "helpline" has been formalized. Email questions sent to namd@ks.uiuc.edu, vmd@ks.uiuc.edu, or mdscope@ks.uiuc.edu, are answered within a business day.

- A mailgroup for users of the VMD program to share information about their work was created. Similar mailgroups for NAMD and MDScope users are being created.

- An internal advisory committee has been helping the MDScope team with identifying needs and directions for future development of the software.

- The first VMD workshop was held on February 13, 1997 (see Appendix 4). The one day workshop offered training in using VMD. The workshop consisted of hands-on tutorials and formal presentations. Subjects included general principles of molecular graphics, the production of high quality images, and scripts for analyzing structures.

- VMD demonstrations and presentations have been offered on- and off-campus in professional meetings, conferences and symposia such as Annual Supercomputing Meetings.

- As part of our ongoing efforts to ensure that our distributed software is up-to-date, useful, and of high quality, we conducted a users' survey in 1996 and will conduct it again in Fall 1997. The survey was specifically designed to determine the needs and level of satisfaction of our users. Three similar questionnaires on VMD, NAMD, and MDScope were constructed and sent electronically to a target population obtained from FTP log files.

- The Resource's workstation clusters are presently used by over 40 external users from on–campus groups as well as outside users such as the Brünger Group at Yale, Board's group at Duke, Pidgeon's group at Purdue, and the Michel group at the Max–Planck–Institute for Biophysics at Frankfurt. Regular external use takes between 10% to 15% of the Resource total disk space. The projected use will be significantly higher in the coming years due to the increasing number of collaborations, the ever growing size of the biological structures studied, and the consequent computational demands.

- The Resource has hosted frequent visitors from collaborative groups and others in the past funding period. The visitors usually stay here for about a week, and their space and office needs are taken care of by the Resource staff. During their stay they use our computational facility and benefit from both the hardware available and software developed here. Recent visitors include:

  - **Chris Sheldahl** (February 1996) Work with NAMD
    University of Alabama at Birmingham
  - **Lars Nyland** (June 1996) Work with NAMD
    University of North Carolina at Chapel Hill
  - **Erick Fredj** (September 1996) Collaboration involving bacteriorhodopsin calculations
    The Hebrew University of Jerusalem

General Services

- The 3D projection facility has been extensively used for scientific, dissemination and training purposes, and for meeting community interest. The facility is regularly included on UIUC tours by federal and state officials, and is operated by the Resource personnel, with demonstrations being made several times a week. Visitors to the facility over the past grant period included R. Marcus (California Institute of Technology), J. Yortner (President of the Israeli Academy of Science), Illinois Board of Higher Education, Illinois Senator Rauschenburger, H. Michel (Max–Planck–Institute, Frankfurt), P. de Gennes (Ecole Normale Superieur, France), S. White (University of California, Irvine), P. Sharp (MIT), S. Ikenberry (former UIUC President), J. Stukel (UIUC president), M. Klein (University of Pennsylvania), S. Schreiber (Harvard), J. Haggin (Senior Editor, *Chemical & Engineering News*, T. Bell (Senior Editor, IEEE Spectrum), M. Bishop (Director of the G. W. Hooper Research Foundation, UCSF), M. Feigenbaum (Rockefeller), R. Friesner (Columbia), W. Gear (Princeton and NRC), S. Okinaga (Chairman of the Board of Trustees for the Teikyo University Foundation and President of Teikyo University), M. Parinello (Max Planck Institute), K. Patel (Vice Chancellor for Research, UCLA), R. Penrose (Rouse Ball Professor of Mathematics, Oxford University), J. Richardson (UNC–Chapel Hill), C. Schmidt (Michigan), E. Shakhnovich (Harvard), T. Von Forster (Editor, Springer-Verlag publishing), J. Widom (Northwestern), P. Woodward (Univ. of Minnesota, SGI graphics director), P. Higgs (University of Manchester), R. Fletterick (UCSF), Leo Groenen (Ludwig Institute, Melbourne, Australia), Valerie Taylor (Northwestern), J. Brickmann (Technical University Darmstadt, Germany). Demonstrations were also held for prospective UIUC faculty, graduate students, high school physics students, our Open House visitors and others.

- Our HTTP server is regularly maintained to give all users of the Internet access to publications, images, and routine activities of the Resource. The average number of unique host accesses per month is about 4,500. The address for our home page is `http://www.ks.uiuc.edu/`.

- The Resource has organized an annual Open House. The yearly event attracts many on-campus visitors, both students and faculty, and leads to renewed and increased interest in our research and development efforts.

- The Resource is the center of a so-called Grand Challenge Application Group funded by NSF. This group includes researchers from Duke (J. Board), Yale (A. Brünger), NYU (T. Schlick), and UNC (J. Hermans). The group's goal is to jointly develop and apply algorithms for large scale and long time biomolecular simulations. The

Resource organizes a yearly retreat for all the researchers involved (Appendix 7.2). The annual meetings provide an ideal setting for the exchange of information and ideas between the five research groups. The 1996 meeting was held in September at NYU.

- The Resource has organized a popular seminar series in theoretical biophysics which serves a wide group of campus researchers and has attracted many speakers.During the past year the following outside speakers have presented lectures in the Resource seminar series at the Beckman Institute:

  Carolina Cruz-Neira, Computer Science Department, Iowa State University, February 26, 1996, Lecture: *Interactive Visual Supercomputing Immersed in Science and Engineering*

  Helmut Grubmueller, Ludwig-Maximillians-Universitaet Muenchen, Germany, March 4, 1996, Lecture: *Protein Dynamics Simulations: Toward Experimentally Verifyable Predictions*

  Michael C. Zerner, Department of Chemistry, University of Florida, April 1, 1996, Lecture: *On the Initial Photochemical Event in Photosynthesis: A Theorist's View*

  Jose' Onuchic, University of California at San Diego, April 4, 1996, Lecture: *Pathway tubes as the building blocks for designing electron trahsfer proteins*

  G. Ludwig Hofacker, Technical University, Munich, Germany, April 4, 1996, Lecture: *Concepts of Biological Information*

  Gyorgy Barna, KFKI Research Institute for Particle and Nuclear Physics of the Hungarian Academy of Science, July 18, 1996, Lecture: *Population Activity in a Statistical Model of the Hippocampal CA3 Region*

  Valerie Taylor, Northwestern University, Evanston, IL, August 13, 1996, Lecture: *Coupling Supercomputing Simulations with Visualization Environments*

  Paolo Carloni, IBM Research Division, Zurich Research Laboratory, September 9, 1996, Lecture: *Toward the ab-initio modeling of biological systems in laboratory-realizable conditions*

  Juergen A.W. Brickmann, Technical University of Darmstadt, Germany, September 12, 1996, Lecture: *Molecular dynamics simulations in systems with quantum and classical degrees of freedom*

  Juergen A.W. Brickmann, Technical University of Darmstadt, Germany, September 13, 1996, Lecture: *Modelling strategies for the treatment of molecular recognition*

Sebastian Reich, Konrad-Zuse-Zentrum, Berlin, Germany, September 16, 1996, Lecture: *Molecular dynamics in the fast lane - How dangerous is it?*

Gisbert Schneider, Free University of Berlin, Institute for Medical/Technical Physics and Laser-Medicine, Berlin, Germany, September 23, 1996, Lecture: *Sequence-oriented peptide design by neural networks and evolutionary algorithms*

Jeremy C. Smith, Centre d'Etudes Nucleaires de Saclay, Gif-sur-Yvette, France, September 30, 1996, Lecture: *Combination of Simulation with Experiment to Probe Biomolecular Structure and Dynamics*

James A. Given, Center for Advanced Research in Biotechnology and Biotechnology Division, NIST, Gaithersburg, MD, October 14, 1996, Lecture: *A First-Passage Algorithm for Brownian Dynamics*

Kim Baldridge, San Diego Supercomputer Center, San Diego, CA, October 28, 1996, Lecture: *A Theoretical Play in Four Acts: Theoretical Study of Reaction Processes with the Incorporation of Solvent Effects*

David van der Spoel, Groningen, The Netherlands, October 29, 1996, Lecture: *Side Chain Dynamics in Proteins and Peptides*

Evan Evans, University of British Columbia, Vancouver, Canada, November 11, 1996, Lecture: *Brownian Dynamics of Molecular Bond Dissociation under Force*

Pamela S. Parkes-Loach and Paul A. Loach, Northwestern University, February 24, 1997, Lecture: *Evaluation of Stabilizing Interactions in the Core Light-Harvesting Complex of Photo-synthetic Bacteria by Reconstitution with Bacteriochlorophyll and Polypeptide Analogs*

Gerald J. Small, Iowa State University, Ames Laboratory-Department of Chemistry, Ames, IA, February 28, 1997, Lecture: *Electronic Structure and Energy Transfer Dynamics of the LH2 Complex of Purple Bacteria: High Pressure - Hole Burning and Theoretical Studies*

Stefan Goedecker, Max-Planck Institut fuer Festkoerperphysik, Stuttgart, Germany, February 28, 1997, Lecture: *Linear Scaling Solution of the Coulomb Problem using Wavelets*

Yvonne Martin, Abbott Laboratories, Abbott Park, IL, March 10, 1997, Lecture: *Computational Tools for Computer Assisted Drug Design in the Absence of Knowledge of the 3D Structure of the Target*

Charles L. Brooks, III, The Scripps Research Institute, La Jolla, CA, March 31, 1997, Lecture: *Exploring free energy landscapes in protein folding*

Professor Felix Izrailev, Budker Institute of Nuclear Physics, Novosibirsk, Russia, April 4, 1997, Lecture: *Onset of Quantum Chaos and Thermalization in*

Systems of Few Interacting Particles

Kent R. Wilson, Dept. of Chemistry and Biochemistry, University of California-San Diego, CA, April 21 1997, Lecture: *Ultrafast X-Ray Diffraction and Spectroscopy*

Michael C. Wiener, Dept. of Molecular Physiology and Biological Physics, University of Virginia, April 28, 1997, Lecture: *X-Ray Crystallography of Membrane Protiens: Issues and Examples*

Paul Bash, Math and Computer Science Division, Argonne National Laboratory, May 5, 1997, Lecture: *Study of the Reaction Mechanism of Malate Dehydrogenase by Computer Simulation*

Training

The training activities at the Resource greatly overlap with the service and dissemination efforts. In addition to the information provided in the previous service section and the following dissemination section, the Resource's Principal Investigators advise graduate students in their respective departments and offer rotation opportunities to undergraduates.

- The Resource organized several workshops and conferences which are reported in the service and dissemination sections.
- The Resource's projection facility was frequently used for Physics, Biophysics and Chemistry classes.
- Long and short term visitors to the Resource, previously mentioned in the service section, benefitted from on-the-job training and hands-on experience with the Resource software, in particular with VMD. The direct and intensive interactions with the software developers and the application scientists, already familiar with the various features, made their stay at the Resource particularly advantageous.
- The Resource maintains a small yet well stocked library. We presently subscribe to 14 periodicals which include titles such as: *Current Opinion in Structural Biology*, *Nature*, *Nature Structural Biology*, *Science*, and *Issues in Science and Technology*. During the past year newly published books were purchased in areas such as quantum mechanics, human genetics, mathematics, biocomputing, protein folding, protein structure, parallel programming, system administration, and neurobiology. We expect to continue to purchase books, to keep our journal subscriptions, and possibly to add new ones, depending on our research needs and availability of funds.

The Resource library is well cataloged. The catalog is available for Resource members on the web (`http://www.ks.uiuc.edu/Group/Library/`), and has become an important training tool for staff members and visitors.

- Much of the research and development activities at the Resource is performed by graduate students. The graduate assistants typically leave the Resource once they complete their education. The list below includes Ph.D. and M.S. recipients, postdoctoral associates and undergraduates who received their training at the Resource during the past year.

  PhD Students

  1. **Thomas C. Bishop**
     Ph.D. in Chemistry, University of Illinois, 1996
     "A Molecular Dynamics Study of Hormone Receptor - DNA Binding"
     Postdoctoral Associate, University of California at Berkeley
  2. **William F. Humphrey**
     Ph.D. in Physics, University of Illinois, 1996
     "Molecular Dynamics Studies of the Protein Bacteriorhodopsin"
     Postdoctoral Associate, Los Alamos National Laboratory, Los Alamos, New Mexico

  Postdoctoral Associates

  1. **Ivo Hofacker** (1995–1997)
     Research Associate, Institut fuer Theoretische Chemie, Waehringerstrasse 17, 1090 Wien, Austria

  Undergraduate Trainees

  1. **Vera Koffman** (Summer 1996–present)
     Undergraduate, University of Illinois, Computer Science
  2. **John Lin** (Summer 1995–present)
     Undergraduate, University of Illinois, Computer Science

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